Medicines for the year 2000

Medicines for the year 2000

Medicines for the year 2000

A symposium
held at the Royal College of Physicians,
London in September 1978 by the
Office of Health Economics

Edited by
George Teeling-Smith
and
Nicholas Wells

162 Regent Street, London W1R 6DD

Printed in England by
White Crescent Press Ltd, Luton

Contents

Session IV

Foreword

Speech to the Symposium Dinner by the Rt Hon Roland Moyle MP

Minister of State for Health

I do not want to trespass into the field of your discussions when there are so many people better qualified than I to contribute. But perhaps I could profitably say a few words about the pharmaceutical industry in Britain at the present time. On reflection this is by no means inappropriate to a consideration of medicines for the year 2000 when one thinks about the extent to which the industry has to plan ahead and the years of research and development which necessarily precede the introduction of an effective and safe medicine. This industry competes in an international market in which success depends critically on innovation. About two years ago a report by the Economic Development Committee for the Chemicals Industry commented that 'the United Kingdom has had a strong, progressive and innovative pharmaceutical industry for many years and it remains one of the major growth sectors of the chemical industry as a whole'. That certainly remains the position today. That the industry shall continue along this line is of vital importance to us all for the year 2000.

I would like to develop this theme and its opportunities but before I do so I want to say that nothing in this world is simple. The industry tends to arouse stronger emotions than most. Whilst some marvel at your technical achievements a not inconsiderable section of the population worries about its potential for harm, as they see it. As a Government and as an industry we shall both have to tread warily if the second emotion is not to overwhelm the first. There will be a constant public trial of the integrity of the industry but by a jury not always wholly impartial. This challenge to the industry will be almost as great as to its technical and commercial ingenuity. And that phrase returns me to my main theme.

In 1977 total expenditure on research and development by the pharmaceutical industry in the United Kingdom was about £130 million; by 1979 I understand this figure is expected to rise to £170 million. Obviously a substantial proportion of that expenditure has still to bear fruit and this wide ranging research is necessarily expensive and carries a high risk; but regularly important new medicines emerge from this investment; and last year was no exception. On average I understand some 20 new products a year are introduced in the United Kingdom; in 1977 we saw the launching by United Kingdom companies of significant new drugs for the treatment of glaucoma, angina pectoris, ulcerative-colitis, coronary thrombosis and many other conditions.

As a result of this innovation, it comes as no surprise that the United Kingdom industry holds such a strong position in the world market for pharmaceuticals and ranks fourth among the world's leading exporters. In 1977 there was a favourable balance of trade in pharmaceutical chemicals and preparations (excluding dressings) of £313 million. I am delighted to hear that the trade in the first half of 1978 shows an even

more encouraging trend. At £304 million for the first six months, exports were £27 million up on the total for the first half of 1977 whilst imports increased by less than 6 per cent to £109 million, leaving a favourable trade balance for the half year of almost £200 million. This is a most splendid effort by the industry as a whole. British-owned companies have a very fine record indeed; but I am sure I do not have to remind this gathering of the invaluable contribution made also by British-based subsidiaries of overseas companies. In this connection it is of interest that the company of which the President of the Association of the British Pharmaceutical Industry is Chairman regularly exports about one-third of its total production. Indeed in 1977 I believe its total exports amounted to some £9.5 million.

When Mrs Barbara Castle, then Secretary of State, congratulated this industry on achieving an export figure of £300 million, she challenged its members to see how quickly they could improve this to £500 million. With so fine an industry record it is not perhaps surprising though none the less gratifying, to find that only three years later this objective should already have been reached.

I congratulate the industry on this magnificent achievement and look forward to even greater things for the future. For a forward-thinking industry there are still more prizes to be won. And that brings us back to the subject of this symposium and to the important educative role played by the Office of Health Economics in helping the British pharmaceutical industry to remain forward-thinking. We all owe a great debt to OHE.

Introduction

The purpose of these introductory notes is to draw attention to the central issues raised during the Symposium and to identify some of the potential gains stemming from the discussion as a whole.

In many ways, the tone of the meeting was set by Archie Cochrane in his opening paper which examined the positive and negative factors affecting health – the 'goodies' and 'baddies' as he called them. He entertained his audience with the 'robust' conclusion that a high ratio of doctors per thousand population was a 'baddy' in health terms – although assuring the audience that the finding must be an artefact. Beyond this, the concept of 'goodies' and 'baddies' emerged once again in the discussion of the role of the pharmaceutical manufacturers and government in promoting continued pharmaceutical innovation.

In this respect, Brian Cromie identified the world drug regulatory authorities as the principal 'baddies'. Current regulations, in delaying the availability of potentially life-saving medicines, are resulting in patients suffering and dying needlessly. He went so far as to refer to the agencies as 'mass murderers'. He further stated that, if current regulatory trends continued at their present rate of growth, his own company, probably the largest pharmaceutical manufacturer in the world, would be forced to abandon all truly innovative pharmaceutical research at some point during the 1990s. He asked 'Will it happen?' and 'Does it matter?'

Many representatives of the industry clearly shared similar misgivings about the current policies and behaviour of official regulatory agencies throughout the world. Specifically and perhaps most significantly there was concern at the potential developments within the European Community. Many felt that the European bureaucrats might merely take individual national regulations and accumulate them into new conglomerate requirements. The effect of this might be to stifle all future development of new medicines within Europe. Henry Grabowski echoed these fears in the context of the United States. He argued that the recently promulgated regulations there might add seriously to the effects of the 1962 Food and Drug Administration amendments in slowing innovation.

However, government representatives from both the United States and Europe showed an awareness of these dangers. It, therefore, seems probable that although the hazards of excessive drug regulation have been pointed out on many occasions before, their repetition with such force at this meeting may have helped to ensure that in the future legislation will be more selectively drafted and more sensitively interpreted. Indeed, representatives of the British authorities at the meeting went out of their way to acknowledge that pharmaceutical innovation is a high-risk activity, and gave welcome assurances that these risks are taken into account in price negotiations in this country at least.

Much discussion was concerned with the suggestion that action by government agencies is, to a large extent, no more than a response to public opinion. In this respect many delegates felt that the industry could only blame itself for having failed to project a favourable and realistic image to the general public. The 'consumerists' still seemed to suffer the

delusion that absolute safety could be achieved for medicines. They had so far failed to recognise that a balance of risks and benefits is just as inevitable in medicine as it is in every other sphere of human activity. Further, it was suggested that the industry had insufficiently emphasised its achievements and had allowed too much limelight to fall on the dangers associated with medication. Public education along these lines was thus clearly identified as a major area of need; but, as Louis Lasagna pointed out, it will require a collaborative effort involving pharmaceutical manufacturers and professional individuals and bodies interested in the health of both society and the industry.

When the discussion turned to pricing Duncan Reekie expanded on his earlier findings and explained that pharmaceutical firms use price as a strong competitive factor in their marketing strategy. His new studies which cover the Netherlands as well as Britain and the United States lend further support to this conclusion. Yet some price regulatory authorities still often seem to base their behaviour on the 'conventional wisdom' that price competition is absent for prescription medicines. The Symposium, therefore, provided an appropriate opportunity for a restatement of Reekie's findings. The latter suggest that pharmaceutical price regulation schemes can now probably only be justified on grounds of *political necessity* rather than as rational economic measures to promote 'reasonable prices'.

The issues inherent in the provision of medicines for the less developed countries (LDCs) generated a discussion of considerable quality and value. Both Sanjaya Lall and Gordon Fryers indicated the need for the multinational companies to have a more creative and sympathetic approach in dealing with the health care problems of the third world. Eric Scowen and Michael Peretz emphasised the complexities and dangers in constructing a list of 'essential drugs' best suited to the requirements of the LDCs. Louis Lasagna drew attention to the conflicts they encounter in deciding on the most appropriate strategy for obtaining their medicines. And, finally, Archie Cochrane put these problems in perspective by pointing out that fundamental improvements in the health of the third world are currently more dependent on advances in areas such as sanitation than simply on the availability of modern drugs.

The Symposium thus underlined many of the difficulties currently faced by the international pharmaceutical industry and the prohibitive consequences they may have for continued pharmacological progress. These problems have of course already received much attention but at this Symposium they were perhaps discussed more fully and frankly – and in front of a wider audience – than has been possible on other occasions. It is to be hoped that government and industry behaviour will be influenced in a favourable manner by the commonsense arguments put forward at this meeting. The creation of an environment in which investment in pharmaceutical research is positively encouraged will be a critical factor in determining whether or not medicines for the many untreatable diseases of today will be available by the year 2000. As Bill Wardell pointed out, the list of 'essential drugs' which the Symposium *should* have been discussing were those for the unconquered diseases such as the cancers, multiple sclerosis and schizophrenia.

SESSION I

Medicines contribution from the 1930s to the 1970s

Chairman *Sir Michael Swann, FRCS*

Thank you, Mr Teeling-Smith. In spite of your kind remarks, I really do not know why I should be opening this. I have come to the conclusion that if there is any organisation or set of organisations which perhaps has more public trouble than drug companies it must surely be universities, and is, and I am sure will continue to be, the British Broadcasting Corporation. I think that is why Mr Teeling-Smith must have felt that I would fit in rather naturally.

Quite apart from that, however, the subject of the conference is an extremely interesting one. It was, indeed, one that I used to touch on many years ago when I used to lecture first-year Edinburgh medical students. One of the things I used to say to them was 'you assume that all the advances in modern medicine have had dramatic effects and it would not be the same without all the drugs we have, but the argument is not quite as simple as you may think', and I used in a simple way to go into some of the difficulties that I think we are going to go over this morning, and very fascinating they can be.

Then, later on, one moves on to an extremely important area: the almost obsessional desire of society, not only in this country but in most countries of the world, to avoid any risks with drugs and whether in fact that is inhibiting progress and piling up considerably greater risks. I do not know quite why society applies that particular form of obsessional interest to the drug companies and pharmaceutical research – more, I would judge, than to almost any other walk of scientific, medical or manufacturing life – but it is a fact that one has to live with and the more it is aired for the benefit of society at large and of governments the better it will be.

Then ultimately the conference homes in on the future and what that may hold clearly depends very much on attitudes to research, attitudes to drug testing, attitudes to price control and all manner of other things.

1931 – 1971: A critical review with particular reference to the medical profession

A L Cochrane CBE FRCP FFCM
Formerly Director, Medical Research Council Epidemiology Unit

My job as I see it is to review the period 1931–1971, paying particular attention to the activities of my profession. The period falls neatly into three contrasted parts; 1931–1939 – a time of slow recovery from a deep depression; 1940–1950 – a time of war and its aftermath, and 1951–1971 – a period of modest affluence, before the next slump.

From a medical input-output point of view, the most interesting contrast is between the first and third periods. Unfortunately quantitative evidence is rather patchy about the first period but it seems probable that, on average, about 1.5 per cent of our Gross National Product (GNP) was devoted to health expenditure in the first period, compared with 4 per cent of a much larger GNP in the third period. The number of doctors and nurses approximately doubled. The internal input clearly increased.

As regards the external 'input' the difference is even greater. In the first period the only innovations were insulin and the sulphonamides while the third period saw the technological revolution – particularly in the pharmaceutical industries. Administratively, too, there was the massive change from the system of free enterprise, tempered by the 'panel' and charity, to our National Health Service (NHS).

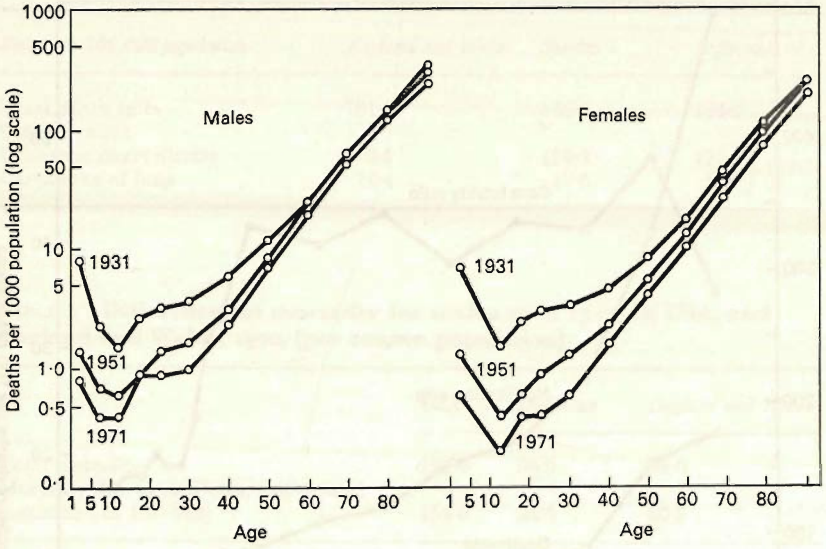
One must not forget the war years – terrible though they were. They gave us penicillin, and improvements in blood transfusion and traumatic surgery. They also made it easier for us to accept the idea of the NHS, and in particular made a salaried hospital service and a capitation based primary care service possible. My travels in the USA, Canada and Australia have convinced me that the 'Fee for item of service' has few advantages for the patient or the tax-payer. On a personal note I would like to add that at least one POW doctor got an excellent education about the relative importance of 'cure' and 'care' and the recuperative power of the human body in the absence of medical intervention.

For 'output' measurements we regrettably only have mortality and to get equality of years I have combined the first two periods (Figure 1).

The decrease in mortality is clearly very much greater in the first period than the second, the decrease being greater for women.

Superficially, it does look as if it would be difficult to explain the contrast between the low input and high output in the first combined periods, and the high input and low output in the last period of modest affluence and an organised health service. However, I think the problem has been more or less solved by recent publications, particularly that by Tom

FIGURE 1 **Death rates in England & Wales 1931, 1951 & 1971**

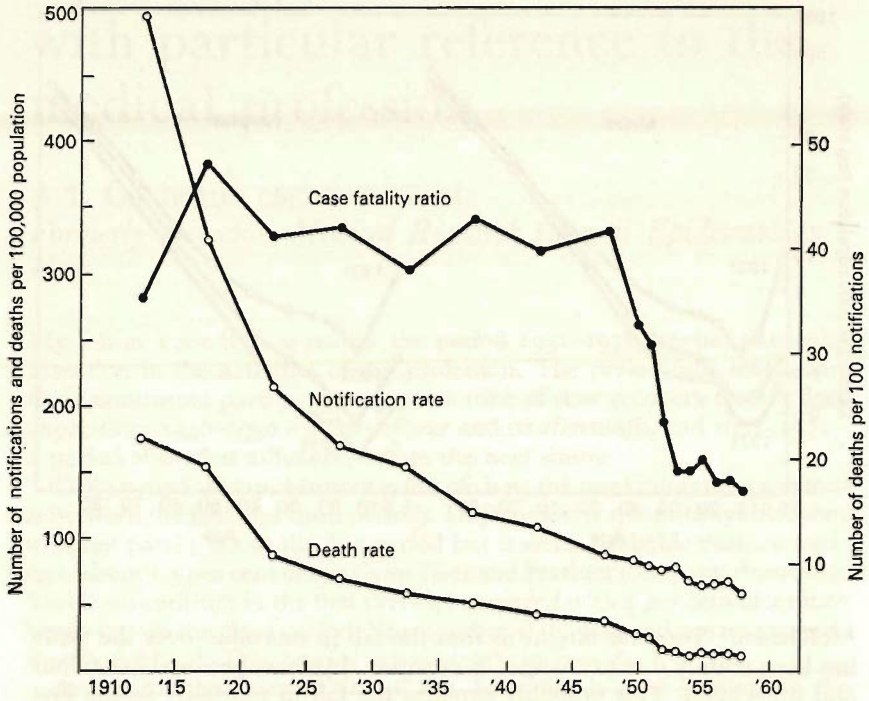


McKeown.[1] Tom has taught us that the fall in mortality over the years has been mainly due to changes in nutrition, hygiene, personal behaviour and prevention. This probably explains the fall in mortality in the first period of low inputs. This tendency would probably have continued into the last period though it would almost certainly have slowed down as the infectious diseases slowly disappeared. This was interrupted by a change in our behaviour, which certainly led to an epidemic of carcinoma of the lung, and very probably to one of ischaemic heart disease. The third factor that affects mortality in this period is the effect of the technological revolution. Attempting to assess the relative importance of Tom's factors, the epidemics, and the new technology, to say nothing of the increased proportion of old people is a fascinating study, but there is nothing really surprising about the end result.

The problem we are most interested in is the effect of medical intervention in this last period especially in relation to its cost. Did the country get value for money? The real trouble is that mortality, the only index available, is the wrong index for this sort of activity. Mortality varies directly with incidence and case-fatality. The effect of preventive medicine is best judged by changes in incidence and clinical intervention by changes in case-fatality, but, unfortunately, comparable information about incidence and case-fatality is very limited for this period.

Figure 2 shows how different the effect of intervention may appear in the field of tuberculosis, when seen from the point of specific mortality or case-fatality (although I have some doubts as to whether I chose the correct denominator). A similar approach in areas where case-fatality can be estimated gives a rather gloomier picture of the results of intervention on carcinomata of the breast and stomach.

FIGURE 2 **Pulmonary tuberculosis in New York City 1910–58**



We all know that there have been real gains in this period of innovation. I don't need to list them here, but we must admit our inability to quantify them exactly in most cases. It becomes therefore impossible to discuss in real terms, the problem that interests us most, as to whether the patient and the tax-payer really got value for money in that third period of high inputs and low apparent output. All that can be usefully said is that the costs of the 'cure' side would have been considerably lower if all the innovations had been carefully evaluated before being introduced. I will return to this point later but for the moment I want, as we are stuck with mortality, to see what we can get out of some international comparisons based on the year 1970, at the end of the period.

The first point I want to make is in connection with a generalisation I think put forward first by Fuchs[2] in his book *Who shall live*, suggesting that differences in mortality are due to specific causes for which the health services treatment are very ineffective. I want to illustrate this with two examples.

The first comes from a comparison between England and Wales and Sweden. Swedish mortality rates are lower than ours in the higher age group. For example in men aged 45–54.

The difference is entirely due to ischaemic heart disease and cancer of the lung, which no health service is very effective in treating. Turning now for contrast to a high cost high mortality country, the USA. Our mortality is

TABLE 1 **Causes of differences in total death rates between Sweden, and England and Wales in age group 45–54**

Rates per 100,000 population	*England and Wales*	*Sweden*	*Difference*	
Total death rates	701·5	536·6	164·9	
Specific rates:				
Ischaemic heart disease	259·1	136·5	122·6	182·5
Carcinoma of lung	77·4	17·5	59·9	

TABLE 2 **Differences in mortality for males aged 15–24 in USA, and England and Wales, 1970, (per 100,000 population)**

	USA	*Difference*	*England and Wales*
Total mortality	192·0	98·0	94·0
Mortality due to accidents, suicide and homicide (AE 137–149)	154·6	94·4	60·2

lower in every age-sex group. For men aged 15–24 the specific causes of the difference are particularly interesting.

The differences apparently relate to how we live, and have little to do with our health services.

These examples are clearly, for the sake of brevity, selected, but I can assure you that I have tried this rather superficial approach on many age-sex international comparisons and always got the same results. I conclude that the differences in mortality between developed countries are in general controlled by how we live and not by the differences between our health services.

If this is true, and I admit it is in no wise proven, it does suggest that all developed countries are getting about the same value, as regards mortality from their health services, and that, if we only differ in mortality according to the way we live, a further corollary of this might be that the lowest spender in this group of health services might be the most efficient – the NHS.

Intrigued by this argument I have recently, with the help of Dr Selwyn St Leger, completed a detailed correlation and regression analysis of the association between mortality in developed countries and a large number of factors likely to influence mortality. The results have recently been published,[3] so I will only here sketch in the details.

Table 3 gives the names of the countries studied (we omitted Japan to make the group more homogenous genetically).

The next table gives the output measurements variables which we used inthe analysis. While the 'input' variables are given in Table 5. The sources for the figures are available in our paper.[3]

TABLE 3 **Countries used in the study**

Australia	Finland	New Zealand
Austria	France	Norway
Belgium	German Federal Republic	Scotland
Canada	Republic of Ireland	Sweden
Denmark	Italy	Switzerland
England and Wales	Netherlands	USA

TABLE 4 **'Output' measurements**

Mortality indices for 1970:
National mortality Infant mortality
Mortality (both sexes) for age groups:
1–4; 5–14; 15–24; 25–34; 35–44; 45–54; 55–64

TABLE 5 **'Input' variables**

Population density	% Health expenditure from general taxation
Education index	Consumption of:
Birth rate	Cigarettes
GNP per head	Alcohol
Doctors per 10,000 population	Calories
Nurses per 10,000 population	Protein
Hospital beds per 10,000 population	Fat
Health expenditure from general taxation	Sugar

The index used is slightly different from the usual. This has been introduced by Dr Selwyn St. Leger. Instead of showing the regression coefficients the figures show the percentage change in the death rate following a one standard deviation change in the input variable, the other variables remaining constant.

The final indices are of course of two kinds – positive (the 'baddies') and negative (the 'goodies'). In the higher age-groups there is little that is surprising. Cigarette consumption as we expected is the main 'baddy', and GNP per head the 'goody' (Table 6).

In the younger age-groups the results are more surprising particularly amongst the 'baddies', where 'doctor density' appears to be the most important.

There are many side-paths that one could explore, but today I just want to draw three main conclusions.

1) What trouble one gets into when one is forced, by one's age, to abandon controlled trials, and forced to use correlation and regression.
2) That there is no evidence that in developed countries increasing any of the Health Service factors (doctors, nurses, beds and health expenditure) has any significant effects in decreasing mortality.
3) The odd findings about 'doctors'.

This is a curious finding. It is very robust. We found it in 1960 as well.

TABLE 6 **Regression analysis of mortality rates on the seven variables with greatest explanatory power**

Mortality Rates	*Input variables with highest positive indices*		*Percentage sum of squares explained*	*Input variables with highest negative indices*	
Maternal	Cigarettes	25	72	Sugar consumption	29
	Alcohol	18		GNP	15
Perinatal	Doctors*	8	90	GNP*	11
	Cigarettes	8		Sugar consumption	8*
0–1 years	Doctors*	17	97	GNP*	16
	Cigarettes	10		Sugar consumption	4
1–4 years	Doctors	3	55	GNP*	8
	Cigarettes	1		Intervention index	6
5–14 years	Cigarettes	5	42	Sugar consumption	6
	Doctors	1		Intervention index	2
15–24 years	Cigarettes	2	79	Intervention index*	16
				Population density	7
25–34 years	Cigarettes	5	65	Sugar consumption	11
	GNP	1		Intervention index	10*
35–44 years	Cigarettes	4	57	Population density	9*
				Intervention index	9*
45–54 years	Cigarettes	7	55	GNP	7
				Population density	4
55–64 years	Cigarettes	7	62	GNP	9
				Intervention index	3

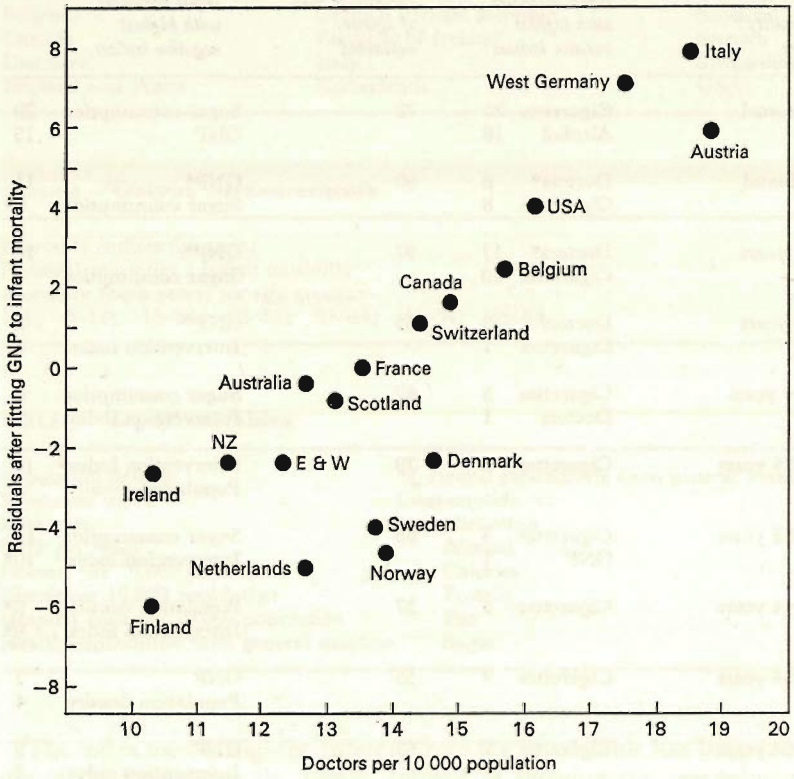
*T value in regression analysis > 2.

It alone explains 45 per cent of the variance. It remains if other developed countries such as Japan and Czechoslovakia are included. In very poor countries the correlation is actually negative, but this decreases as countries become more developed. The correlation becomes negative at about a level of 10 doctors per 10,000 population.[4] The most striking evidence in favour of the relationship is seen in Figure 3. Here the residual factors affecting infant mortality (after plotting the regression on GNP per head) has been plotted against doctor density. The linear relationship is very striking.

I personally believe it to be an artefact, (though I am obviously biased), because we have not been able to repeat the finding when examining similar data for the states of the USA, or the regions of the UK. But it certainly needs explaining.

This led me to consider what the medical profession actually did in the periods we have previously considered. What can we say about the first period? Let us be clear from the start that we have no way of knowing whether the 'caring' aspect of the profession has improved or not, and I

FIGURE 3 **Relationship between infant mortality and doctor provision in 18 developed countries, allowing for gross national product/capita.**



consider this as, at least, the equal of 'cure' in our profession's duties. (I would guess that we are now rather more humane.) As regards 'cure' in the first period the simplest generalisation is that we interfered too much, particularly surgically. Few children in social class I and II retained their tonsils, and few males in those classes retained their foreskins. Many others in all social groups lost their teeth in the fight against focal sepsis. I remember operations for constipation and ptosis that I would rather forget, and I understand there were some odd operations on the peripheral nerves. On the medical side the worst aspect was probably the consolidation of the idea that every medical complaint deserved a bottle of medicine or a packet of pills, with the disastrous consequences we still face, and in a minor way, there were many who were condemned unnecessarily to lives of inactivity on the basis of a systolic murmur at the apex. In a sense the profession cannot be criticised as there was no satisfactory technique of evaluation available, but the lack of interest in controls is rather disturbing.

Throughout both periods, though mostly the second, there is another general criticism that can be made against the profession, namely that we misled developing countries, particularly when our colonies became

independent. We tended to sell them modern hospital medicine instead of persuading them to complete the sanitary revolution, which the colonial powers had barely started. We sent them neuro-surgeons rather than sanitary engineers, with disastrous results.

In the last part of the period it becomes somewhat easier to judge the profession. The randomised controlled trial became available. The profession has a primary duty to its patients to help discover the most effective therapies. If we accept, as I think we must, the fact that the only institution that can decide on the percentage of GNP that should be spent on our health services is a democratically elected government, then it is surely the profession's second duty to see that the country gets maximum value for money. We cannot do it alone. We need the help of economists in particular and others, but we can play a vital role in measuring the effectiveness and efficiency of what we do. It is therefore not unreasonable to judge our profession and its specialities by the use they have made of the randomised controlled trial (RCT) technique.

In the first place we were in no great hurry to use it. Florence Nightingale wrote in 1858 'The first requirement of a hospital is that it should do the sick no harm', but it wasn't until 1971 that the first controlled trial comparing home with hospital treatment was published.[5] Similarly many members of the profession must have enjoyed Asher's jingle, in 1947:

> 'Teach us to live that we may dread
> unnecessary time in bed!
> Get people up and we may save
> Our patients from an early grave!'

and yet it wasn't until 1967 that the first controlled trial of 'length of stay' and early mobilisation appeared.[6] (I have here omitted any mention of the Tb trials. I discuss them later as a special case.)

I next played with the idea of ranking all our specialities according to the extent they had used RCTS to evaluate what they were doing and the extent to which they acted on the results, but I had to give up the idea. The main reason was the difficulty of getting the data. It is surely a great criticism of our profession that we have not organised a critical summary by speciality or sub-speciality, up-dated periodically, of all relevant RCTS. (Perhaps the Office of Health Economics would finance it!)

I decided finally just to award a first prize (a 'Bradford' if you wish in praise of Bradford Hill) and a wooden spoon. In attempting this I must ask your indulgence as I am conscious of the unequal opportunities and difficulties the various specialities have had in carrying out such trials, as well as my own limited knowledge and almost certain biases.

As regards the 'Bradford', there is fortunately one sub-speciality to which I can give almost unlimited praise – that disappearing breed in this country – the Tb chest physicians. Every new drug has been carefully examined both as regards effect, alone and in combination with others, dosage toxicity, length of treatment and cost. Place of treatment was randomised early. Nearly all the Tb physicians in the country helped in the trials, and acted on the results, although they knew they were working themselves out of a job. Some of them continue to help the rest of the world.

It was a magnificent achievement. I have no hesitation in awarding them the 'Bradford'.

Of course they were lucky. The scarcity of streptomycin and the persuasive power of Bradford Hill got them started. There were plenty of Tb cases. They were working within the NHS. They had satisfactory reproducible objective outcome measures, and they were superbly led.

The wooden spoon was more difficult to allocate. I first considered the psychiatrists. It is true they have rather failed to evaluate psycho-analysis, psycho-therapy and the psycho-tropic drugs. But they have tried and their difficulties are enormous with no objective end-points and the difficulty of avoiding bias even in double blind drug trials.

I then considered surgeons. They have certainly done very few trials in comparison with physicians, but they have real psychological difficulties. It is so much easier to randomise pills than operations. I have, too, a great admiration for the trials done by British surgeons comparing radical and simple mastectomy, eg[7], and for the excellent way all surgeons reacted to the results of the trials, particularly when they are compared with American surgeons.[8]

So I turned to the cardiologists. The case against the cardiologists is simply their unwillingness to evaluate the Coronary Care Unit (CCU), which was and is an expensive, resource-consuming technique. I was present at the Platt Committee which adjudicated on Mather's proposal and was surprised by the thinness of the evidence put forward to justify the use of this very expensive therapy which they then hoped to offer to all IHD suffers. The late Lord Platt apparently agreed when he decided Mather's proposal was ethical. Mather's first publication was met by a conspiracy of silence. Much later criticisms of the trial were published.[9] These related (a) to poor design. Given the ethical constraints imposed I doubt if any of those who signed the document would have done any better; (b) to the low percentage of the incident cases available that were randomised. This was almost entirely due to the stringent ethical constraints imposed. It is also surely only fair to point out that no other trial, so far as I know, attempted to randomise all the incident cases in a group of GP practices. (c) The third criticism referred to the lack of definition and follow-up of those not randomised. This seems to me unreasonable. I know of no trial which does it better. (d) The fourth criticism related to the interval between the onset of symptoms and the first medical contact. The critics complained that it was too long. I think this is completely answered in Mather's second paper.[10]

Mather's trial is not perfect. Very few are. But if the cardiologists were dissatisfied why didn't they do a better one? They had, and have a clearly defined duty to do so. The rest of the profession, and the public still want to know who should with advantage be admitted to a CCU.

But to be fair the cardiologists have done particularly well in carrying out trials of 'length of stay' and 'time of mobilisation' for example.[6, 11, 12] In this area the British cardiologists probably lead the world. I therefore reserved judgement until I had examined the gynaecologists and obstetricians.

The latter have a distinguished past. The Confidential Inquiry in Maternal Mortality and the British Perinatal Mortality Surveys are, for

instance, models for all time, but the speciality seems to have slipped up more recently. The speciality missed it's first opportunity in the sixties, when it failed to randomise the confinement of low risk pregnant women at home and in hospital. This was followed by a determined refusal to allow 'Pap smears' to be randomised, with disastrous results for the whole world. Then having filled the emptying beds by getting nearly all pregnant women into hospital, the obstetricians started to introduce a whole series of expensive innovations into the routines of pre and postnatal care and delivery, without any rigorous evaluation. The list is long but the most important were induction, ultra-sound, foetal monitoring and placental function tests. The speciality reached its apogee in 1976 when they produced 20 per cent fewer babies at 20 per cent more cost. G & O stands for gynaecologists and obstetricians, but it could also stand for GO ahead without evaluation!

After due thought and meditation (but without prayer) I awarded them the wooden spoon.

Let me hurry to add that my spies tell me there will soon be a torrent of evaluation in this field. Let us hope that some of these bright ideas will prove as effective as their progenitors believed.

The general effect of this survey is depressing. I was particularly struck by the lack of control over new processes and operations compared with the restrictions on new drugs.

It is with some relief that I turn to a comparison with other countries.

Here once again I can be lavish with praise. The distribution of controlled trials in the world is very skew. They are done almost exclusively in the Protestant north and west and very little in the Catholic and communist south-east. I am convinced after visiting the various capital cities concerned, there are no idealogical or religious reasons for this dichotomy, I suspect it's basically due to the north-west giving a slightly more scientific medical education. But the fact remains that Scandinavia does relatively few trials, and the USA can't do many trials because of private patients, fee for item of service, and a terrifying 'consent' form, so the UK does far more trials, per 100,000 of the population, or per 1,000 doctors than any other country in the world. (I have no figure to support this, but I have said it so often in so many countries, without correction, that I'm beginning to believe it.)

The curious result is that the UK, having graciously surrendered an empire, has assumed a new 'white man's burden', doing controlled trials for the rest of the world. It is enormously to the credit of our profession that we have carried this burden so long. It is to be hoped that others will soon play their part.

Let me summarise my final opinion by quoting one of my own reports from school. Surprisingly I was very good at maths at school (at Uppingham), and found myself the youngest in the form, but easily capable of being first or second in the class without working. I used the time to read nineteenth-century novels: I thought I had fooled the master. But the report came 'Has done well, but could do much better if he tried'. I was furious that he had seen through me. I hope that my colleagues will not be so angry if I give them a similar report: 'We have done well, but we could have done very much better if we had tried harder.'

REFERENCES

1 McKeown T (1976). The role of Medicine, dream, mirage or nemesis? Oxford University Press, Oxford.
2 Fuchs V R (1974). 'Who shall live?'. Basic Books, New York.
3 Cochrane A L, St. Leger A S and Moore F (1978). *Journal Epid and Com Medicine*, 32, 3.
4 Gilliand P and Galland R (1977). World Health Statistics Report, Vol 30, No 3.
5 Mather H G *et al* (1971). *British Medical Journal*, 3, 334.
6 Groden B M *et al* (1967). *Scottish Medical Journal*, 12, 435.
7 Atkins Sir H *et al* (1972). *British Medical Journal*, 2, 423.
8 Bunker J P *et al* (1977). Costs, Risks and Benefits of Surgery. Oxford University Press, New York.
9 Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society (1975). *Journal Royal College Physicians*, 10, 1, 5.
10 Mather H G *et al* (1976). *British Medical Journal*, 1, 925.
11 Royal Infirmary Glasgow (1973). *Lancet*, 1, 346.
12 Harpur J E *et al* (1971). *Lancet*, 2, 1331.

Changing patterns of disability – the processes of transition

David Taylor
Deputy Director, Office of Health Economics

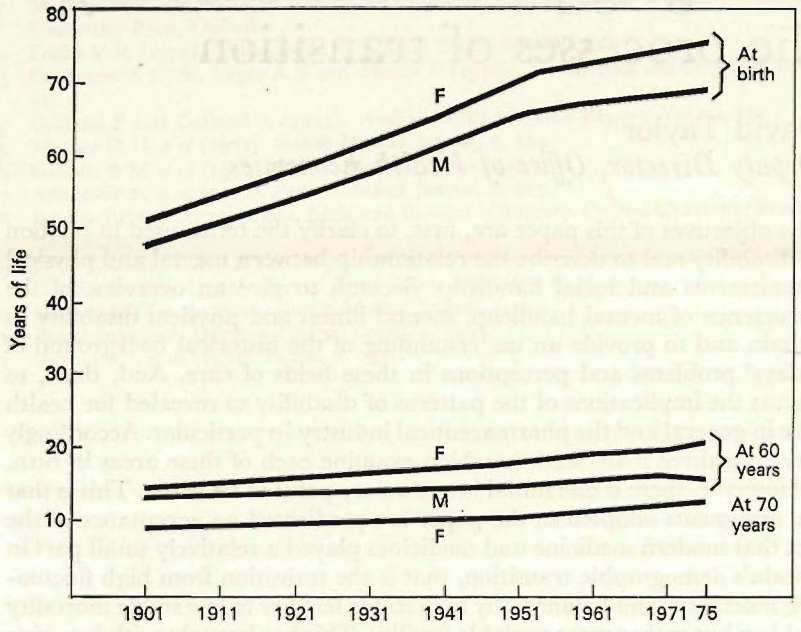
The objectives of this paper are, first, to clarify the terms used in relation to disability and to describe the relationship between mental and physical impairments and social handicap. Second, to give an overview of the occurrence of mental handicap, mental illness and physical disability in Britain and to provide an understanding of the historical background of todays' problems and perceptions in these fields of care. And, third, to discuss the implications of the patterns of disability so revealed for health care in general and the pharmaceutical industry in particular. Accordingly there are three main sections which examine each of these areas in turn.

However, there is one initial introductory point to be made. This is that the arguments adopted in the paper are predicated on acceptance of the fact that modern medicine and medicines played a relatively small part in Britain's demographic transition, that is the transition from high fluctuating mortality rates balanced by high stable fertility to low stable mortality and low but rather more variable fertility. This has brought with it ageing of the population (a relative increase in persons in their 50s and over as compared with the numbers of children), the pattern characteristic of 'developed' nations. Pharmaceutical products like the antiobiotics and hormonal contraceptives, together with immunising agents, made a genuine contribution to the end stages of this process. But social and economic changes in fields like housing, diet, sanitation, education and attitudes to fertility behaviour were the central motors of change.

The significance of this observation is that demographic transition was intimately associated with disability transition, a fundamental shift in the nature of the predominant causes of physical and to a lesser extent mental disabilities in our community. In absolute and relative terms there has been a decline in the numbers of people either impaired from birth or disabled early in life by diseases such as tuberculosis. Conditions like multiple sclerosis and schizophrenia which typically manifest in the second, third and fourth decades of life now stand out, together with phenomena like the thalidomide tragedy, as glaring exceptions to the general rule that most people will survive their first forty or fifty years free of major disability. Yet they survive to experience subsequently a high risk of impairment from chronic degenerative conditions like stroke, coronary disease, senile dementia, Parkinsonism, bronchitis and most prevalent of all the rheumatic disorders.

Not infrequently this rise in the prevalence of chronic disabling conditions is seen as a consequence of the power of modern medicine to keep people alive. But this interpretation is false. Even in the case of the diseases of the very elderly, like senile dementia, the main factor has simply been survival to the begining of later life, not extensions of life

FIGURE 1 **Life expectancy in Britain in 1901–75**



Source Registrar General

expectancy bought about after people have reached their sixties or seventies because of the use of medicines (see Figure 1). Rather the main effect of medicines has been to improve the quality of life, to alleviate distress and facilitate rewarding activity, of people who because of changed social factors would anyway have lived to face distressing impairments. And equally the main effects of advances in fields like obstetric care and traumatic surgery in the last fifty years have, on the weight of the evidence available, been to reduce the incidence of disabling impairments rather than simply to extend the lives of handicapped babies or young people.

The conclusion to draw from this is that it is not simply in the future that, failing the advent of techniques which radically extend life expectancy, professionals like doctors and agencies like international pharmaceutical companies should see the prevention and alleviation of potentially disabling conditions as their central role. It is probably already their main achievement, difficulty to quantify though this assertion may be.

It is against this background understanding that the first main section of this paper, on the terminology of disability and handicap, is approached.

Terms and models

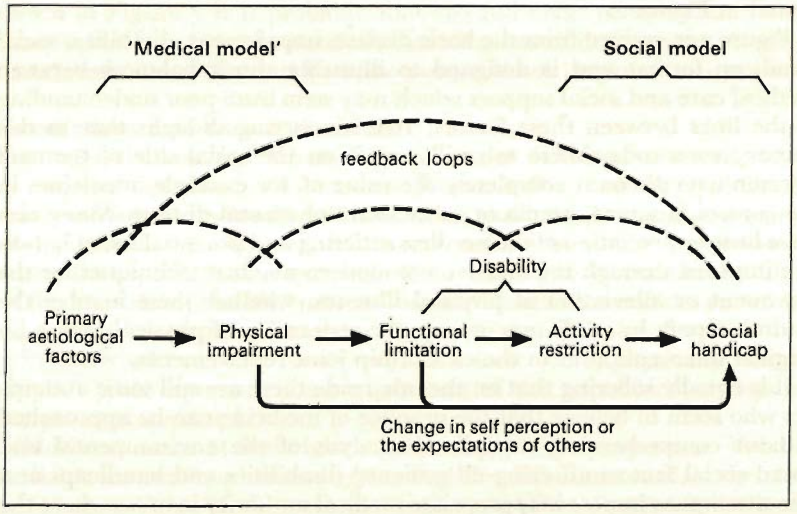
Figure 2 shows one possible schema for the precise use of terms which in everyday language have rather vague general applications to describe in detail the relationship between bodily impairments and associated social handicaps. It is based on the work of Dr Philip Wood and his colleagues at the Arthritis and Rheumatism Council's Epidemiology Research unit. Alternative models exist (see OHE 1977) which in some circumstances are

more appropriate but overall this is probably the best available. It may be applied to physical limitations and to both mental handicap (limitations of intellectual ability) and mental illnesses.

Primary aetiological factors include phenomena like infections or genetic or chromosomal abnormalities which may give rise to impairments. The latter range from tangible defects like a malfunctioning joint or overt brain damage to less easily observable factors like postulated biochemical lesions in, say, schizophrenia and manic depressive psychoses. Impairments lead to functional limitations, such as loss of gripping power in rheumatoid arthritis, and so in turn to activity restrictions, like not being able to climb stairs in cases of arthritis or severe bronchitis or being unable to do, say, simple money calculations in cases of more serious mental retardation. These may in the final analysis promote social handicap, in which the affected individual fails to find a satisfactory way of life, to achieve the social contacts, occupation, independence or income which the person concerned considers to be within the bounds of acceptability.

Consideration of this model leads to a number of useful conclusions about 'disability' and the links between bodily impairment, social handicap and the objectives of medical and other forms of rehabilitative care. For example, it may be seen that at the impairment and functional limitation levels the problems to be dealt with are essentially mechanical. The objectives of preventive or remedial treatments, whether these involve surgery or the use of medicines, may be understood within what is popularly regarded as the traditional 'medical' model of illness.

FIGURE 2 **Disability – the basic model**



Note In the case of mental distress the feedback between the socially handicapping consequences of psychiatric impairment and disability may be complex in that social variables sometimes act as primary aetiological factors. Also in practice the psychiatric sequelae of physical disability can have a major influence on social determinants of rehabilitation like the capacity of the individual to build or maintain supportive personal relationships.

Activity restriction is, however, rather more governed by factors related to personal resolve and motivation. As well as the rational choices individuals may be able to make about how to cope within the limited options open psychological readjustments and rehabilitive training designed to help people relearn old skills or acquire new ones are of central value. A medical diagnosis and prognosis is still of major importance in deciding appropriate paths of action but even at this stage many essential aspects of rehabilitation are not 'medical', at least in the sense indicated above.

Finally, when social handicap is considered a broad spectrum of factors beyond the individual come into play, including cultural attitudes to mentally or physically less able or distressed people and the opportunities which normal day-to-day life has to offer such persons for achievement. Here purely social observational techniques like those based on deviance theory, the analysis of interaction networks and illness behaviour models have a real contribution to make to understanding the handicapping consequences of impairments.

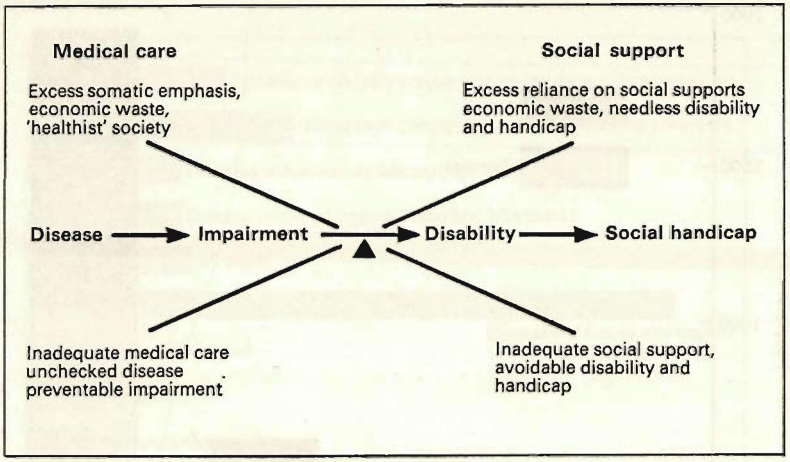
The differences between the latter and attempts to understand disability based on the traditional 'medical' model of disease may to some people appear so great that they can see only conflict between the two sides. For instance, the study of schizophrenia provides clear examples of the fragmentation of professional understanding of a disabling disease, just as it also provides examples of how individuals' social identities may be destroyed by the existence of functional limitations and consequent activity restrictions in the field of social interaction. But in fact, as Professor John Wing (1978) has recently argued, most incompatibilities between 'medical' and 'social' views of mental and physical disease and consequent disability may be resolved by the adoption of the type of approach suggested in Figure 2.

Figure 3 is derived from the basic disease, impairment, disability, social handicap format and is designed to illustrate the imbalances between medical care and social support which may stem from poor understanding of the links between these factors. It is a sobering thought that in this country even today there are still people on the social side of the care fulcrum who discount completely the value of, for example, medicines in the control of schizophrenia or other forms of mental distress. Many also have little appreciation of the needless suffering and potential social handicap imposed through the underuse of modern medical techniques for the treatment or alleviation of physical illnesses, whether these involve the control of pain by medicines or, say, the restoration of physical ability by surgical intervention as in the case of hip joint replacements.

It is equally sobering that on the other side there are still some authorities who seem to believe that the practice of medicine can be approached without comprehensive, disciplined analysis of the environmental and broad social factors affecting all patients' disabilities and handicaps and who attempt to impose inappropriate medical authority in areas where the best interests of people receiving care obviously relate to improved social, educational and allied provision. Mental handicap is one area capable of providing examples of such thinking (see OHE 1978).

In conclusion to this first section, therefore, it may be argued that many of the ill-informed and intellectually unacceptable attacks made in rela-

FIGURE 3 **The care balance**



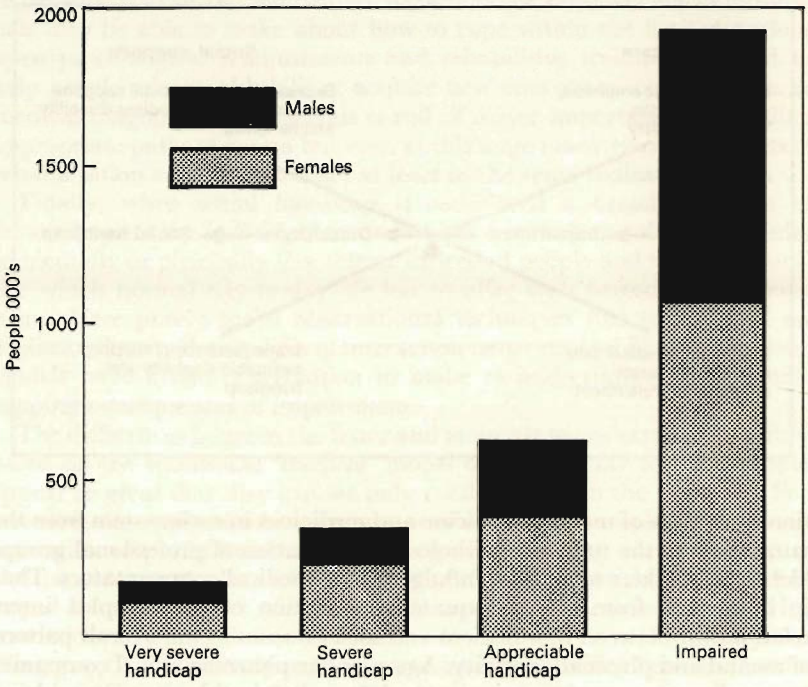
tion to the role of modern medicine and medicines in society stem from the same roots as the unjustified wholesale denigration of professional groups like social workers sometimes indulged in by medical commentators. That is, both stem from an inadequate appreciation of the complex inter-relationship between bio-medical and social factors in the overall pattern of mental and physical disability. Agencies like pharmaceutical companies have a direct interest in improving understanding in this area. For without increased public and professional acceptance of the type of simple model shown in Figure 3 it is probable that the full value of medicines in the treatment of any type of potentially disabling condition from, say, diabetes to depression or asthma to Parkinsonism, will not be practically realised.

Occurrence and care transition

Figure 4 is derived from the findings of a major British government survey on physical disability, conducted in the late 1960s (OPCS 1971). It found that in all some three million adults living outside institutions have significant physical impairments, well over a million of whom have to some degree the capacity for independent self-care in a domestic context. Adding on the numbers of disabled persons living in institutions and the size of the child disabled population one can derive an estimate of 1·5 million individuals who may be considered, in a loose sense, physically 'handicapped'. This represents some 3 per cent of the population, as against 6–7 per cent impaired.

This may seem at first sight a surprisingly high proportion. Yet the available international data suggests that the definitions used in the OPCS survey were tight. If, for example, indicators of occupational disadvantage related to disability had been used as has been the case in surveys conducted by the US Social Security Administration, the percentage of handicapped people would have been raised significantly. It might also be noted that in some areas, especially that of sensory impairment, there was serious under-recording. Data from other sources suggests that

FIGURE 4 **Handicapped and impaired adults in the community**



Source Handicapped and Impaired in Britain, HMSO 1971

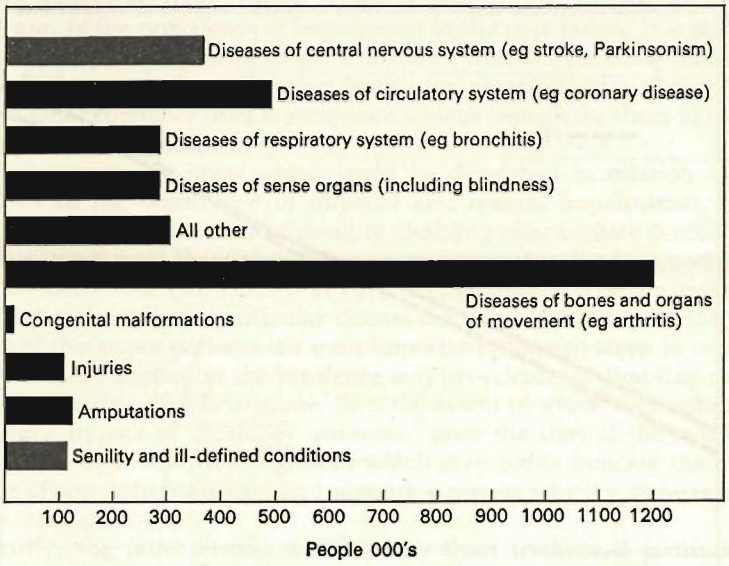
approaching 4 per cent of the total population is affected by deafness alone (DHSS 1976).

Figure 5 illustrates the predominance of chronic degenerative diseases of middle and later life as the causes of physical impairment in the adult population. And Figure 6 shows that the rate of impairment rises exponentially with age. In fact some two-thirds of all significantly physically disabled individuals are over retirement age and of the remainder a majority are in their fifties and sixties.

However, the available figures on mental handicap and the various forms of mental illness show a rather different pattern of occurrence. In the case of mental handicap recorded prevalence (ie administrative prevalence) peaks in the mid-teens, because it is at this stage that mentally handicapped people are most 'visible' to authorities like education departments. In all severe mental handicap affects only about 150,000 people in the UK (around 0.2–0.3 per cent of the total population) whilst more arbitrarily defined mild mental handicap affects in the order of 2 per cent of the total population. (In some other western countries, a much larger proportion is regarded as being in the mild mental handicap or learning handicapped categories – up to 10–15 per cent).

As regards the mental illnesses the between disease variations in occurrence patterns are much greater and hence aggregate presentations of data are of less value. The incidence of neurotic disturbance is high –

FIGURE 5 **Major causes of physical impairment in adults outside institutions**



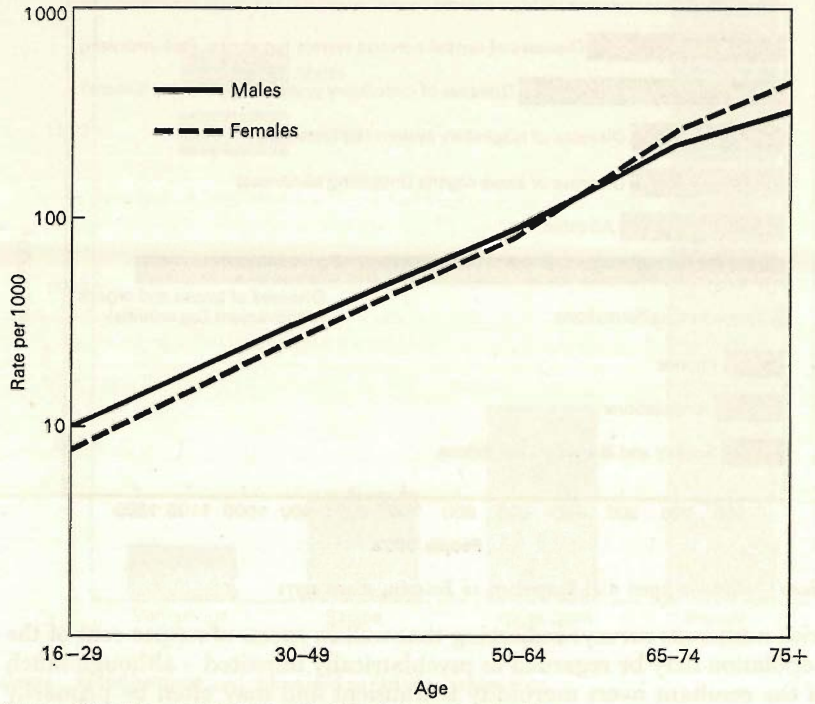
Source Handicapped and Impaired in Britain, HMSO 1971

with numerous surveys indicating that well in excess of 20 per cent of the population may be regarded as psychiatrically impaired – although much of the resultant overt morbidity is transient and may often be primarily related to external social variables rather than underlying genetic or allied individual factors (see Brown and Harris 1978). There is still very little satisfactory data on the amount of long-term limitation and social handicap generated by psychiatric distress conventionally regarded as being of a less serious nature and normally treated outside hospitals.

Yet even the volume of potentially disabling psychiatric illness referred to secondary, specialist, care is very considerable. Judging by recent British experience approaching 1 person in 10 will receive inpatient psychiatric treatment during their lifetimes. About one per cent of the total population will at some time be diagnosed as schizophrenic of whom only around one-third will recover to a state of fully non-disabled function. (The equivalent American diagnosis figure is over 2 per cent of total population). A similar proportion will be diagnosed as manic depressive. And of the population aged over 75 some 15 per cent suffer senile dementia or associated severe mental infirmity. Including the less serious cases there are probably over 600,000 mentally infirm older people (DHSS 1976).

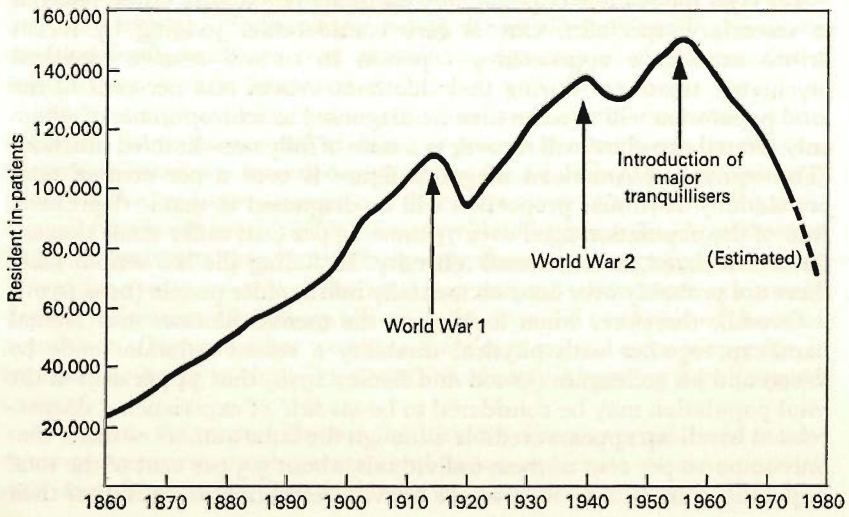
Overall, therefore, when looking at the mental illnesses and mental handicap together with physical disability a recent estimate made by Wood and his colleagues (Wood and Badley 1978) that 34 per cent of the total population may be considered to be 'at risk' of experiencing disease-related handicap appears credible although the same authors estimate that only some 10 per cent of these individuals, about 3.5 per cent of the total population, are in a state of severe activity restriction as a result of their

FIGURE 6 **Age specific impairment rates per 1000 people in the community**



Source Handicapped and Impaired in Britain, HMSO 1971

FIGURE 7 **In-patients resident in mental illness hospitals – England and Wales 1860–1978**



impairments. The suggestion that a third of the entire population is 'at risk' of being considered disabled may seem absurd but the data presented above shows that there is good reason to regard this estimate as a valid indicator of the prevalence of impairment in the population. It is perhaps a measure of the success of modern medicine that despite rising and often unrealistic expectations of perfect health the great majority of people do not in fact experience disease symptoms serious enough for them to regard themselves as disabled.

There are many areas which could be developed in relation to this analysis of the occurrence of physical and mental impairments. They range from an examination of possibly disabling effects which professional interventions may themselves have on patterns of individual and community behaviour (see Illich *et al* 1977) to investigations of the impact of medical technology in particular disease contexts. However, for the purposes of this paper perhaps the most important points to stress in relation to available statistics on the incidence and prevalence of disabling conditions in countries like Britain are, first, the extent to which they reflect the dramatic impact of 'disability transition' since the start of the twentieth century and, second, the degree to which they today indicate the emergence of new patterns of care and support, a process which may be referred to as 'care transition'.

Briefly, the latter entails a shift away from traditional institutional patterns of segregated care for groups like the mentally handicapped and the mentally ill coupled with a growing awareness that in the field of chronic illness what is needed is frequently long-term coordinated medical care and social support rather than 'once off' treatment and retraining. The full extent of the need for such domiciliary-based 'maintenance rehabilitation' has only been recognised recently, partly because in much of the developed world modern rehabilitative services were first set up to cope with the large numbers of traumatically injured young men generated by the First and Second World Wars.

The most striking illustration of the initial stages of care transition is provided by the figures on the mental hospital inpatient population, which in England and Wales began to decline in the early 1950s, as shown in Figure 7. This reversal of the upward trend of the past century or so coincided closely with the introduction of the first of the major tranquillisers. Data from many other countries reveals very similar experiences.

It would be too simplistic to claim that new medicines alone were responsible for this fundamental shift in mental health care which occurred in the early 1950s. Other social and economic factors were involved. Nevertheless, the power of drugs like chlorpromazine to alleviate some psychotic symptoms and to protect sensitive individuals from the ill effects of stressful situations, notably those family relationships characterised by high levels of expressed critical emotion (Brown *et al* 1972), was a highly important variable. It could be argued that in some senses the major tranquillisers catalysed a broader process of social change related to what this paper terms care transition. The realisation that interventions aimed at one level of the disease, impairment, disability, social handicap chain may have subtle indirect effects at levels other than those at which their direct action takes place is central to the following discussion on the

implications that changing patterns of disability have for health care in general and the pharmaceutical industry in particular.

Implications for the future

Britain's experience of disability is not unique. The figures available from most other industrially developed countries are very similar, as are the organisational problems they face. Even in countries like Japan, where demographic transition was relatively recent and relatively swift, the changing structure of the population is bringing with it patterns of chronic illness and disability similar to those of Europe and North America.

Many less developed countries still have high fertility rates and thus a high proportion of younger persons in the population. They also have high prevalence rates of infective and parasitic conditions like tuberculosis, leprosy, malaria and schistosomiasis. But even in this context it is likely that Britain's experience of 'disability transition, may provide useful lessons regarding the tasks that health and allied social services in such countries will face in the not too distant future. Advances in fields like immunology coupled with accelerated processes of fertility reduction could mean that by the middle of the next century the entire world will have undergone or be undergoing the disability transition that Britain has seen in the last fifty years or so.

There are a number of areas from which such lessons may be drawn. For example, one already noted is that related to concerns that there already may be an excessive professionalisation of care and support for the disabled. Coupled with this there are fears that more and more peoplemay be sucked into the net of disabled people entitled to special services as a result of a 'numbers game' played out between pressure groups, politicians and others vieing for attention, kudos and power. Together such trends could lead to the type of disabling society described by writers like Illich. Despite the fact that the models he proposes may be considered extreme it would be unwise to discount them altogether. For example, Illich's view of iatrogenesis may on examination be seen to be related to more scientifically testable concepts like Seligman's (1975) model of 'learnt helplessness' and Brown and Harris' (1978) sociological research into hopelessness and loss of self-esteem as the social roots of depression,

However, there is no easy means of ensuring the avoidance of the possible side effects of well-meant legislation and professional activity. A balance between too much and too little intervention in the day-to-day lives of ordinary people can only be approximated through vigorous public debate about what services are trying to achieve and at what cost. Further a clear line cannot be drawn between the disabled, deserving of special assistance, and the non-disabled who have to compete in society normally. Rather situations have to be met as effectively as possible when they arise within the general understanding that wherever possible 'normal' community life and values should be capable of tolerating wide ranges of variation in individual physical and mental ability and performance. Thus a minimum number of people will be singled out as being in need of 'abnormal' help.

Following on from this point a second area where useful lessons may be drawn from Britain's experience of disability is that of employment

rehabilitation. For instance, it now appears that some of the past emphasis on helping people to take part in 'normal' industrial work could have become inappropriate because 'normality' itself is changing. Certainly for the future the increasing automation of many production processes and consequent reduction of labour needs means that more emphasis should be placed on the importance of service industry and domestic or allied community activity. In fact given the age structure of the disabled population it may well be that much more effort should be put into rehabilitation for worthwhile retirement although the economic and allied problems associated with creating a desirable flexibility in this field are such that there is a tendency amongst policy-makers to shy away from it.

A third area is that of the effect of changing patterns of disability on the structure of the health service. The analysis presented in this paper, can be used to cast light on the difficulties confronting not only the NHS but the health care systems of all developed countries. For example, the problems of the sophisticated interprofessional and interagency interaction needed to link efficiently care on the traditional 'medical model' level to activities aimed at the prevention of social handicap explain much of the concern about professional status and authority found amongst doctors and other health workers. The linking of strictly 'medical measures' with other forms of social and economic support has also multiplied the difficulties inherent in measuring the efficacy of alternative patterns of care and so determining resource allocation priorities. Such phenomena underly many of the complex structural and procedural provisions of the reorganised NHS, provisions which have in turn helped to generate new sets of problems (see OHE 1977).

More specifically the policies which have emerged in the last two decades of closing larger, segregated hospitals for various groups of mentally disabled people are illustrative of the process of 'care transition' initiated by 'disability transition'. The unlocking of the caring skills previously confined to such institutions and dispersing them in the community is in part an adjustment to the economic and social pressures generated by the latter.

Now that most people live for a time unimpaired but have to face a high probability of experiencing physical disability in later life and now that better scientific understanding has for the informed at least demystified mental illness and destigmatised mental handicap the community is less tolerant of old standards and patterns of care. But the costs of switching from the established order to potentially more acceptable arrangements have included public confusion and doubt together with some overt hostility, perhaps especially on the part of people in the health service who fear that their careers might be adversely affected.

The ways in which needless conflict and distrust can be generated in the wake of public uncertainty and ill-informed criticism may be well illustrated in the final area this paper examines in relation to disability, the use and further development of modern pharmaceuticals. It is sometimes argued that the 'pharmaceutical revolution' was a short-lived event which is now at a close. Often allied to this belief is the equally falacious one that modern medicines, and the advances in fields like surgery which they facilitated, have generated as much illness and disability as they

prevent in as much as they only postpone suffering so that it might be experienced in the extra years of life gained. An implication of such views is that with the benefit of past experience it might be better to concentrate resources exclusively on developing adequate general caring services and not to put money into pharmaceuticals or innovations which at best only 'put off' the need for basic care and do so at the cost of driving up the expense of health systems.

All the above suggestions are based on an inadequate understanding of the changing patterns of disability in our community. For example, it was noted in the introduction that demographic transition would have occurred without the advent of modern medicine and that it would have brought with it much the same pattern of disability that we are experiencing today. International comparisons and specific disease studies do not bear out the hypothesis that modern medicine and medicines have in any significant way generated disability. Rather they have actively contributed to the reduction of the total years of impairment experienced in the average lifetime and opened the way to disability and handicap prevention. Although it is not the purpose of this paper to produce a catalogue of the areas in which such progress has been made OHE publications of recent years have amply illustrated this point.

Further, the suggestion that the 'care cost' explosion has been exclusively caused by high technology medicine or the use of medicines to, in individual cases, prolong life is not correct. Demand for care is the key variable in this context, not so much the nature of medical techniques available. Given the non-medical developments of the last century or so care costs in the economically developed world would anyway have tended to rise absolutely with and relatively faster than growing gross national products. One of the motors behind such a trend has been the disruption of traditional community support for elderly or disabled people during the population shifts accompanying urbanisation and industrialisation. Another has been the change in the ratio of young to old people related to demographic transition. And a third is the spread of more humane atittudes towards those disadvantaged by physical or mental impairments coupled with greater expectations on the part of those affected.

All would have probably been present without the emergence of sophisticated medicine and medicines. Although the latter do have significant costs they have at least helped not only to control or alleviate some forms of disability but also to make care transition, the move of the central focus of care away from resource hungry institutions, a possibility. And the outlook for the future regarding the 'pharmaceutical revolution' is that improved medicines for treating or preventing every major disease group mentioned in this paper, from rheumatoid and osteo arthritis to malaria and from schizophrenia to senile dementia, will very probably emerge providing sufficient research effort is made.

Thus, in conclusion, it may be asserted that a full understanding of the changing patterns of disability in modern societies confirms the future potential of new pharmaceutical and other modern medical techniques to act alongside increasingly sophisticated social interventions as partners in a pattern of comprehensive care designed to affect each point of the disease, impairment, disability, handicap sequence. The barriers to the

emergence of a fuller understanding of the role of medicines and scientific medicine in helping people with disease-related social difficulties do not stem from inherent economic or technical problems. Rather they arise from exclusive models of the social as opposed to medical aspects of the disability process coupled, perhaps, with individual failures to adopt a sufficiently pragmatic view of the conflict between humanity's supra-physical aspirations and the finite bodily limitations which beset us all.

REFERENCES

Brown G W, Birley J L T and Wing J K (1972), *British Journal of Psychiatry*, 121, 562, pp 241–58.

Brown G W and Harris T (1978). Social Origins of Depression. Tavistock Publications, London.

DHSS (1976). Priorities in Health and Personal Social Services in England. HMSO, London.

Harris A I, Cox E and Smith R W (1971). Handicapped and Impaired in Great Britain, Part 1. HMSO, London.

Illich I, Zola I K, McKnight J, Caplan J and Shaiken H (1977). Disabling Professions. Marion Boyers, London.

OHE (1977a). Physical Impairment: Social Handicap. OHE, London.

OHE (1977b). The Reorganised NHS. OHE, London.

OHE (1978). Mental Handicap. OHE, London.

Seligman M E P (1975). Helplessness: On Depression, Development and Death. Freeman, San Francisco.

Wing J K (1978). Reasoning About Madness. OUP, Oxford.

Wood P H N and Badley E M (1978). *International Rehabilitation Medicine*, 1, 1, pp 32–37.

The contribution of modern medicines 1930s to 1970s

Sir John Butterfield, OBE, MD, DM, FRCP, HonLLD, HonFACP
Regius Professor of Physic, University of Cambridge

Since Hippocrates, the physician's prime concern has been to help his patients: that is really the beginning and end of it, whether or not the medicines the doctor uses are approved of by society at large, or Health Service treasurers in particular, and it's really no good anyone asking the present generation to abandon this long-standing approach to medicine, even if the whole idea of high technology medicine is under a cloud, as it seems to be today.

You see, I am taking it that we are met here to reflect on what we doctors are all about now, just after the valuable shake-ups we've received from Cochrane, Illich and McKeown and others.

I intend to take a broad brush – a largely British brush – to modern medicine and begin by saying I believe the reason so many medical people were aggravated and frustrated by the Cochrane–Illich–McKeown type of attack was because they felt that the statistics they needed to support the day-to-day work they were doing, concerned with attempts to re-establish the quality of life, were simply not available.

Cochrane asked us: 'Are you sure that what you're doing is doing the good you claim?' I think it fair to say that surgeons have responded with particular vigour to him, both here and in the United States. Perhaps in America peer review has been stimulated by rising labour costs and legal intervention but, in general, this process of peer review is easier for set pieces of surgery than for the medical care of the chronic debilitating diseases which confront most of us physicians, with all the variations in the time of presentation of the case, in the course and in the complications which may arise. Paul Beeson made this point firmly in his own riposte to Tom McKeown's publication. However, I don't think any of us would wish to defend modern medicine by reference to the difficulties which beset us. I believe we prefer to face the challenge, demand better information, use the controlled clinical trial and stand our ground.

Middle-aged medical specialists are particularly conscious of the remarkable change in the hospital scene in the course of their own careers, from deaths on the hospital ward from diphtheria, meningitis and pneumonia through to the development of innoculation programmes and antibiotics; or from the deaths we saw from renal failure, with patients covered with uraemic frost, to renal dialysis and transplantation; or from losing fellow medical students from tuberculosis contracted on the hospital wards, as John Keats contracted it in the nineteenth century, to the present situation where few students are ever exposed to tuberculosis and those who do contract it can be treated.

In the city where we are met this morning, the Hospitals' Cup was a device invented by Medical Deans to make their young people leave the

wards and get out into the fresh air after winter.

Of course, we were all well aware of these remarkable changes. We saw them going on, but we forgot that our achievements were on an inconspicuously small scale compared with the total trends going on outside our hospitals, the trends reflected in national mortality statistics.

How then should we, a small and numerically insignificant profession, defend ourselves, if indeed we must? Paul Beeson sprang to defend modern medicine. The President of this College has responded too, with his Harveian lecture 'Cui Bono? Who benefits?' Do we need to defend ourselves further?

If you read and re-read Illich, or indeed the Director-General of WHO, Hafdan Mahler, a self-styled 'revolutionary doctor', it is difficult to disagree with their general philosophies, that patients, and people, should not be encouraged by doctors, or by society, to expect more than their society can afford, and we must recognise that other professions, particularly the newer disciplines often struggling for well deserved attention and support, resent medicine's power of appeal for resources particularly when they are slender.

One hears that some members of those professions have not been displeased to witness the recent assault on modern medicine's reputation by Illich, McKeown and Cochrane, but the medical profession, like the great amoeba it is, absorbs important ideas and changes. It does not despair or die. I believe good professions must breed elements of self criticism, be outraged by the 'pups' they spawn, react to them, albeit slowly, sit up, bandage the corporate ego, convalesce, rehabilitate, and move on again, though in a different way.

I maintain these occasional jolts improve us by preventing encrustation in reactionary attitudes. So I thank ABPI, and George Teeling-Smith in particular, because they make innovation their business and so do Mahler, Illich, Cochrane and McKeown, though without the same emphasis on the pharmaceutical industry as is given by those of us who use its products as a major source of help in our work.

Of course pharmaceutical developments must be ethical, and controlled and kept under surveillance in terms of the safety, efficiency and purity of the product, as enshrined in the Medicines Act of 1968. Both Cochrane and the others must not be surprised if we believe we practice better medicine now than we did, and give credit to those who led the way and helped. The advance, small scale compared to the totality of human suffering though it may be, has been based more and more on clinical trials, which are now so much better controlled, so much more often double-blind, compared with the experiments in the 1930s. Indeed we have come to practice medicine largely based on foundations in clinical pharmacology and clinical pathology. No, our critics must not be surprised if they find us anxious to defend those who developed the vital cures. Banting and Best's work on insulin became a practical reality for diabetics when the Eli Lilly Company came into the picture. Indeed, doctors both in and outside pharmaceutical companies have frequently been colleagues in rather harrowing experiences, for example during preliminary trials of drugs, especially their administration for the first time to man. So, come St Crispin's Day, some academics will bare their scars with them. Today's

Agincourt strikes me as a better place to be than yesterday's Pharmacopoeia.

How am I to defend what we're about in terms of all these pharmacological and pharmaceutical developments over the last forty or fifty years? Let me begin by giving what I regard as an apt text from the Spanish philosopher, Ortega Y. Gasset. It comes from a collection of his essays 'The Revolt of the Masses'. Gasset was very conscious of and eloquent about the way 'the masses' benefit from the efforts of the few: philosophers, scientists, technologists, leaders. He put his views colourfully, saying (my translation) 'It is as though the great mass of people were lifted up on the shoulders of the intellectual giants* of the past, lifted up quite oblivious of the giants on whose shoulders they were standing'.

To get a feeling of the recent giants on whose shoulders we are all standing today, one may look for the observations of one's predecessors –I was immediately helped in my task today by the inaugural lecture by a former Regius Professor of Physic, Sir Lionel Whitby, 'The Science and Art of Medicine' in 1946. His theme was the then fast growing power of modern therapy. He dwelt on one aspect of therapy which few of us today in the ordinary medical wards consider very often, syphilis. I quote Whitby, 'The medical student of today can have little idea, except from pictures, of the horribly disfiguring lesion of tertiary syphilis, which Ehrlich's Salvarsan has banished from our midst. I myself have seen very few, but I do remember a repulsive lesion of the face, mis-diagnosed as leprosy – which disappeared almost within a week of beginning Salvarsan treatment, to the great annoyance of the eminent dermatologist who, for a long time, had used the patient as a classical demonstration of typical leprosy'.

And, of course, it is not only syphilis that has become a curable disease, but this case does illustrate what physicians want to say in self-defence, namely that modern medicines have improved the quality of many lives.

How? Modern medicines themselves stand on a series of discoveries, and one way to find the giants, those who have been judged to have made the most significant contributions by peer review, is to look briefly at lists of prizewinners.

On the international scene, a glance at the lists of winners selected by the Nobel Prize Committee for Medicine and Biology – which canvasses widely for proposals – reveals how often the work of Nobel Laureates has had major effects on clinical work and therapy (Table 1). I go back to what the Americans regard as the beginning of scientific medicine, the discovery of insulin by Banting in MacLeod's laboratory in 1921 which won them the Nobel Prize in 1923.

Take, for example, the work of Kendall and Hench on cortisone. It not only altered the therapeutic approach to collagen diseases and our understanding of them but, incidentally, quickened our hopes of immunosuppression.

Another relevant list in terms of the practical impact of research is that of winners of the Royal Society's Mullard Award, where the assessment includes the value of the development to the country as a whole, including

*I am prepared to concede that the word 'giants' can be regarded as meaning many persons in a team rather than a single man or woman.

TABLE 1 **Some Nobel Prize winners in physiology or medicine whose work has already affected medical treatment**

Year	*Winners*	*Research field*
1923	Banting, Macleod	Insulin
1929	Eijkman, Hopkins	Vitamins
1934	George Hoyt Whipple George Richards Minot William Parry Murphy	Liver in PA
1944	Henrik Carl Peter Dam Edward Adelebert Doisy	Vitamin K
1945	Alexander Fleming Ernst Boris Chain Howard Walter Florey	Penicillin
1950	Edward Calvin Kendall Tadeus Reichstein Philip Showalter Hench	Adrenocortical hormones
1952	Selman Abraham Waksman	Streptomycin
1954	John Franklin Enders Thomas Huckle Weller Frederick Chapman Robbins	Polio Virus
1959	Severo Ochoa Arthur Kornberg	DNA RNA Synthesis
1960	Frank Macfarlane Burnet Peter Brian Medawar	Acquired immonological tolerance
1962	Francis Harry Crompton Crick James Dewey Watson Maurice Hugh Frederick Wilkins	Molecular Structure of DNA
1966	Charles Brenton Huggins	Hormonal treatment of prostatic cancer
1968	Robert W. Holley H. Gobind Khorana Marshall W. Nirenberg	The DNA and Protein Synthesis
1971	Earl Wilbur Sutherland	Mechanism of Hormones

TABLE 2 **List of winners of the Royal Society Mullard Award**

Year	*Winners*	*Research field*
1967	Dr G. D. H. Bell	Proctor Barley
1968	Professor Pilkington	Glass
1969	Mr R. M. Clarkson	Aircraft
1970	Mr S. W. K. Morgan Dr E. S. Woods Mr J. Lumsden Mrs B. G. Perry	Zinc Blast Furnaces
1971	Dr R. Batchelor Mr F. P. Doyle Dr J. H. C. Naylor Dr G. N. Rowlinson	Semi synthetic penicillins
1972	Dr W. R. Boon	(diquot-peniquot)
1973	Professor C. W. Oakley	Scanning Electron Microscopy
1974	Mr F. B. Mercer	Netlon Net
1975	Mr J. Bingham	Winter wheat
1976	Dr G. H. Hitchings	Trimethoprim, allopurinol azothioprine
1977	Dr G. N. Hounsfield	EMI Scanner
1978	Dr J. W. Black	Beta and H2 Blockers

judgement of commercial success. Note the three awards for developments of new pharmaceutical products (Table 2).

We don't need to go further in our hero-worship to reassure ourselves as a profession that important advances have been made in medicine, advances judged comparable to those in other sciences. What Illich and the other critics have been saying is that we shouldn't be dazzled by all this nor lulled into a state of false security or false pride. We didn't win the prizes personally, and the question is, have we been able to use the fruits of this work satisfactorily as a profession? In other words, how can we judge the practical impact of the research discoveries in pharmaceutical terms, not only on our individual patients in a Hippocratic way, but for society generally?

To get things into perspective, I suggest we look at the scale of the therapeutic developments and the risks they involve compared with the risks of modern life around us.

For the purpose of this paper, I attempted a comparison of 'natural' death rates with those due to medicines and in what follows I am indebted to my colleagues in the Medicines Division of DHSS, to whom I pay tribute and in particular to Dr William Inman. He has studied closely adverse reactions to drugs through the Adverse Reactions Sub-Committee, chaired by a Fellow of this College, Professor Cranston, as part of the operations of the Committee on Safety of Medicines, which is chaired by another Fellow of this College, Sir Eric Scowen.

The crude data suggest that there are about 18,000 licensed medicinal products (excluding herbal mixtures), containing some 3,000 active ingredients. The data sheet compendium issued by ABPI lists over 2,000 products, containing 800 different active ingredients manufactured by 122 companies.

For their good effects on the quality of life, it is probable that most of you can vouch for some benefit from some drug. The question is, the balance between good and adverse effects.

Over approximately the last ten years, Inman and his colleagues have received and reviewed 54,000 reports of adverse reactions to prescribed medicines. Their findings covering 600 products have been summarised and tabulated in three yellow bound volumes entitled *Register of Adverse Reactions* now generally available in medical libraries.

Inman's latest suggestions to me are that there must be between 600 and 6,000 (the lower and upper estimated limits) deaths associated with prescriptions in the NHS each year. Whether it is right to assume that the under-reporting of deaths is the same as the under-reporting of less serious reactions (1 in 10) is not known, but the suggested upper figure of 6,000 seems unlikely to be an under-estimate.

How can we relate these estimated deaths to exposure to medicines?

Inman suggests we assume that the 400 million prescriptions each year cover an average period of three weeks.* With these assumptions we can work out in a crude way the death rate resulting from receiving an NHS prescription – and the answer is 25 to 250 deaths/million prescription years per annum.

* If in fact they cover less time, the final death rate can be multiplied up accordingly.

It can be deduced that being 'in the set of NHS prescriptions taken' is not as risky as being in many other sets. Even being in the set of men over 60; or of women over 70 years of age is perhaps 10 or even 100 times as risky. And being a sick person in those age groups must be even riskier, making it more reasonable still to take a medicine for your illness if it offers you a prospect of improving the quality of your life.

In his important paper, 'The Acceptance of Risk', Pochin[1] sets out age-specific death rates in England and Wales for natural causes from which the figures in Table 3 have been abstracted.

He also gives the United Kingdom fatality rates, expressed per million workers/years, for various occupations. A selection of these, from the lowest rate towards the highest rates of occupational hazards, is shown in Table 4.

For the USA, the rates of four industries, selected from the lowest to the highest quoted by Pochin, are given in Table 5.

Of course the rates were higher where specific chemical hazards obtained as the examples drawn from Pochin's data make clear (Table 6).

But while I conclude that modern medicine does not need to be ashamed of its medicines, we still have to face the other general criticism that we are too hospital and treatment orientated.

Earlier I introduced the idea that a profession like medicine absorbed such criticisms as have been levelled at it recently about its general ineffectiveness and was probably improved by this sort of assault. Pinocytosis of criticism leads to purification of the amoeba's protoplasm.

TABLE 3 **Death rates per million population by age and sex, England and Wales**

	Death rates per annum	
Age (years)	*Males*	*Females*
61–65	25,500	12,300
66–70	43,000	20,000
71–75	69,000	25,000
76–80	106,000	62,000
81–85	151,000	104,000

TABLE 4

	Fatal accident rates
	deaths/million persons/year
Industry clothing and footwear	3 ± 1
Paper, printing and publishing	28 ± 2
Bricks, pottery, glass, cement	75 ± 5
Metal manufacturing	136 ± 5
Shipbuilding	182 ± 8

TABLE 5

Industry	*Fatal accident rates deaths/million persons/year*
Trade	90
Services and Government	135
Construction	739
Mining and quarrying	1,055

TABLE 6

Occupation	*Cause of fatality*	*Death rate deaths/million persons/year*
Shoe industry	Nasal cancer	130
Wood machinists	Nasal cancer	700
Viscose spinners (ages 45–64)	Coronary heart disease (excess)	3,000
Rubber mill workers	Cancer of the bladder	6,500
B naphthylamine workers	Cancer of the bladder	24,000

Changing the idea content of any profession happens unconsciously or noisily. It is more likely to occur if any critical propositions appeal to the younger members of the profession; their view will ultimately prevail anyway. Scrutiny of the medical profession and attacks on its self-satisfaction already seem to be having salutary effects. In the same way as the bacteriologists of the nineteenth century went out from their laboratories into the community and improved sanitary services, there is growing application of laboratory-based medical sciences in community situations today. Community-based or orientated scientific projects reflect the medical profession's growing concern with wider issues which our critics challenged us to consider.

First may I refer to Sidney Cohen's work which has just been rewarded by his election to Fellowship of the Royal Society. An MRC-based protein-chemist-immunologist before he took the Chair of Chemical Pathology at Guy's, Cohen has been looking into the possibility of using a vaccine to interfere with the life cycle of the malaria parasite, in collaboration with the Wellcome Foundation.

About a third of the world's population is still exposed to malaria – there are estimated to be 150 million cases a year. The mortality in Africa alone is one million a year, mainly among children. There has been a serious recrudescence of the disease in parts of Asia and Central and South America: eradication methods reduced the incidence in India to 100,000 cases per annum in 1966 but this has risen to over six million cases in 1977.

The sequence of merozoite invasion of the red blood cells starts with contact between the merozoites and the host red blood cells. The specific attachment of the apical region of the merozoite is to red cells receptors. In the case of plasmodium vibrax this receptor site is related to the Duffy blood group. The attachment induces endocytosis by the red cell and in

one minute the merozoite has shed its coat inside the red cell and is differentiating into the ring form. Plasmodium Knowlesi malaria kills the rhesus monkey, and animals vaccinated with parasitized red cells also die within about a week. Animals vaccinated with a merozoite preparation developed low grade transient parasitaeminia but cleared the infection from the blood completely in due course, and survived. This is medical collaboration between the Medical Research Council, a teaching centre and the pharmaceutical industry which may bear fruit in relief of death and suffering on an immense scale outside these Isles.

I hasten to say that there is similar concern elsewhere for world health problems in stimulating important research; for example at St Bartholemew's Hospital very good work is going on into leprosy.

My last example is also in applied molecular biology, this time the community care of a disease at the other end of the spectrum, a relatively rare condition, haemophilia. Colville at The London Hospital, Katherine Dormandy at the Royal Free Hospital and their colleagues reported regional co-ordination for the care of haemophilia in domiciliary practice in an article which appeared in the *British Medical Journal* last year. When the North East Thames Region appointed a nursing sister to work on haemophiliacs, facilities for home treatment were rapidly expanded. To cater for all the haemophiliacs in the region a network of associated centres were set up in addition to the four main haemophilia centres in the south-west corner of the region.

The home treatment of haemophilia became a practical possibility when the missing Factor VIII – normally a very labile molecule, with a half-life in man of twelve hours – became available in a concentrated form in preparations of known potency which could be stored. All the haemophiliac family needs is a good general practitioner, a refrigerator and a telephone! So far 20 per cent of the London Hospital haemophiliacs are treated at home for their incidental bleeds and, since bringing these services into the community, the work and school records of young cases have improved. Cover is available in the event of dentistry or sports injuries, abrasions at school and, of course, if there is any question of minor surgery.

Turning to the question of expense, 250 units of Factor VIII are needed for each treatment generating a cost of about £25. This compares very favourably with the estimated cost if there isn't such home based early prophylaxis – a hospitalised case costs about £10,000 whereas on average home treatment costs about £2,000 per patient per year.

Here then are the bare bones of a development project which centres on the Blood Transfusion Service, two Teaching Hospitals and the General Practitioners involved.

Of course there is increasing extension of the management of chronic disease using modern medicines from the hospitals and hospital outpatient clinics into Health Centres. There has been especially vigorous action in this matter with the establishment of general practice diabetes mini-clinics which aim to improve diabetic control and reduce diabetic complications.

I suppose a last example of modern medicine in the preventive role might be taken directly from one of the Pharmaceutical industry's recent

successes: the development of chromo-glycate for the treatment of asthma. This certainly has brought remarkable relief to two boys in a community I know very well. In earlier times they might easily have been uncomfortable, handicapped school children requiring attendance at special schools. Although I gather schools for asthmatic children are still open, it is clear to the parents that a great therapeutic triumph has found its way into the community practice of preventive medical care.

My thesis has been that, if our profession is properly motivated, meetings like the present one are welcome opportunities to review how we've absorbed reasonable criticisms, fortifying ourselves with the research of the rising generation, including that going on so effectively in the pharmaceutical industry, where most of the present action is, and modifying our objectives.

This last happens automatically in a free profession which can recruit good people from a free society. The rising able members, as I have indicated, associate themselves with appropriate new objectives and lead us there with the passage of time. Therefore so long as we recruit open-minded students who embrace the Hippocratic notion that the physician's prime concern remains to help his patients, whoever they are, the profession will remain effective and in good heart.

If you want to change the philosophy of the medical profession you must convince the young members of your case – fail in that and your cause is lost. Even if you succeed, expect change to take a long time until the new conviction works its way through the whole profession.

By contrast, if you find a new cure, changing the profession's behaviour will *not* take long. It must be a real cure, a safe cure, but once the profession is convinced, it will be a legal risk to neglect it. So I believe modern medicines have a future.

REFERENCE

1 Pochin, E E. *British Medical Bulletin* (1975). 31, 84.

Discussants

SIR DOUGLAS BLACK *(President, Royal College of Physicians, Britain)*

I believe, Sir Michael, the matters we are discussing this morning might be reduced, though of course with a certain loss, to one central paradox. On the one hand the benefits potentially available from modern medicine have never been greater, and they are certain to increase still further. On the other hand, the systems for what – in a phrase I do not particularly like – is described as the delivery of health care have never been under sharper criticism. I would like to declare myself as a convinced supporter both of medical advances and of our National Health Service.

I have little to add to John Butterfield's spirited defence of modern medicine, but it might help a little if one analyses medical advances into three types. First, there are those which with comparatively small economic expenditure lead to actual cures, although that is a word I use with diffidence in Archie Cochrane's presence. Examples have already been given by John Butterfield, but I can recall the time – and my memory goes back as long as Archie's – when a diagnosis of sub-acute bacterial endocarditis, if correct, was a death sentence. This is no longer true.

Then there are a number of methods of palliating disease which, while not cures, are still economically thoroughly valid. Diabetes and pernicious anaemia have already been mentioned, I would only add to that the many forms of hormone replacement. Jane Austen would not have died young if Addison's disease had been treatable in her day. The trouble really comes from what one might call expensive palliative measures. In my own field of chronic renal failure, dialysis and transplants are expensive procedures, but nevertheless people are alive who would otherwise be dead.

Then there are the coronary care units on which Archie touched, and I think I can explain the resistance of cardiologists. If a cardiologist sees someone's heart stopped as a result of ventricular fibrillation, and started again by defibrillation, if he has seen pump failure setting in as a result of bradycardia and the patient recover when a pacemaker has been inserted, he is a little resistant to the idea that he has not done any good.

If I can turn to the National Health Service, it has one very useful function, it provides through the Office of Population Census and Surveys the kind of figures of which Archie makes such splendid use. More important still, however, I think the great contribution of the health service has been to disseminate throughout the country a good standard of medical care which previously was available in comparatively few places. The extension of high quality clinical care into smaller places in the country seems to me to be the great contribution of the health service.

Of course, all is not well. I very much agree with Sir Francis Avery Jones who said that to some extent we have lost our way in the health service. I think this is not peculiar to the health service, it is one of the by-products of inflation and hung governments and so on. I do not think we should regard ourselves as peculiarly disadvantaged.

Although the benefits of the National Health Service are very great,

there is one thing they do not include, and that is immortality, hence these tears.

PROFESSOR T. McKEOWN *(University of Birmingham, Britain)*

Mr Chairman, ladies and gentlemen, discussions of this type often take the form of an argument between scientific medicine and something else. I think that is a false way of looking at it. What is in question is the value of two different approaches, both scientific, one concerned with disease origins and the other with disease mechanisms. Since both are needed, what is in question is the balance between the two and, if possible, identification of the circumstances in which each is likely to be affected.

Several speakers have recognised that there is not much room for disagreement about the past. The transformation of man's health since the eighteenth century was due essentially to the decline of the infections. The infections declined primarily, not because of intervention in disease processes, but after modification or removal of the conditions which led to their predominance. These conditions were the aggregation and expansion of populations, poor hygiene and insufficient food.

It is one thing to make this assessment of the past and quite another to extrapolate to the future, from the problems of the infections to the residual problems which are essentially those of non-communicable diseases. However, we can get some help from considering the most fundamental question about health which, remarkably, is not often asked. Why does disease occur?

It occurs for one of two reasons: because something has gone wrong with genetic programming at fertilisation or because the individual, correctly programmed, is exposed as embryo, foetus or newborn, to an environment for which the genes were not adapted. Hence the problems of disease fall into two classes, one comprising conditions determined at conception, which are relatively intractable, and the other in which there is in principle the possibility of intervention through modification of the environmental component.

However, there are obvious difficulties in translating what is possible in principle into practice. In some diseases, for example, schizophrenia and multiple sclerosis, we do not know the nature of the environmental influences. In others such as coronary artery disease, the influences are multiple and so difficult to disentangle one from another. In some they are fairly well understood but technically difficult to control, as in malaria and schistosomiasis. In still others the measures required are expensive, as in the case of accidents and many hazards in industry. Some involve modification of behaviour (such as smoking or excessive drinking) which people are reluctant to accept. But the most formidable difficulties arise in respect of influences which are prenatal, as in the examples of mental subnormality and the congenital malformations.

How much does this assessment help us? It identifies an area in which the traditional biomedical approach is uniquely necessary, that is in respect of problems determined at fertilisation. With them I would also group most abnormalities which result from prenatal influences. For the

rest, however, there is at least the possibility of prevention through control of disease origins, as in the case of the infections. However, the traditional biomedical approach will undoubtedly be needed with many diseases in the long period before we discover how to prevent them.

Finally, I would like to refer to a point mentioned by several speakers – the limitations of mortality as an index. It is quite true that it is not a sufficient basis for assessment of medical achievement; it is even less adequate for discussion of the medical role. We must consider not only the prevention of death but also its postponement and the treatment of morbidity. That having been said, it is important to put it into perspective in relation to the other indices, and this can be done by considering the following question. Suppose a parent were asked to choose between two possibilities for a newborn child: that it should experience the improvement in expectation of life which has occurred since the eighteenth century (from about 30 years to nearly 70), with the reduction of morbidity associated with the diseases that have declined, but be denied all other medical care; or alternatively that it should have the medical care, but return to the expectation of life of the eighteenth century, with a high probability of death in the first few years of life.

I do not believe that any thoughtful person would be in doubt about the answer.

Mr M. TIEFENBACHER *(President, IFPMA, Zurich and Bundesverband, Frankfurt)*

Mr Chairman, ladies and gentlemen, I believe it was the Chinese sage Confucius who said that experience was a book that everybody wrote but nobody read. With this wise saying in mind, I feel it was a most gratifying experience this morning to have a panel of expert speakers to show us the medical progress of the last 30 or 40 years and to review to what extent new drug therapies have revolutionised medicine.

I must say I was quite impressed to listen to the views of these outstanding experts and to hear to what extent these new drug developments have benefited mankind. If we take Confucius seriously – and I certainly do – we must open another chapter in the book of medical history. I mean the chapter dealing with the motor of this innovative process. What has set this motor in motion? What was the social, economic, medical environment that made it possible for the industry to develop all these new pharmaceuticals? More important still, to compare the environment of the thirties, forties and early fifties with the environment of today, with the environment – and I hope I shall be forgiven – which specifically the pharmaceutical industry meets today. Do we still have the incentive oriented marketplace that motivates private industry to go forth with courage and zeal, investing risk capital in long-term research efforts? Do we have the type of environment that will stimulate the pharmaceutical industry to bring forth medical progress of a similar dimension in the forthcoming decades as they had in the forties and the fifties?

I think we would all feel a little uneasy if we were called upon to answer this question, as the environment I was speaking of has undoubtedly

changed. It has changed considerably, dramatically, worldwide and all for the worse.

At the roulette tables at Monte Carlo – God forgive us – blue chips have the highest value and anyone risking blue chips expects blue chips in return if he wins. This is only logical, it is only fair, as all of you will agree; if you invest big money in risky ventures, you want at least to have the chance of winning big money back. I am neither a gambler nor an economist but I daresay that this rule would also apply to the world of economics. But my question is: is it still valid of the R and D efforts of the pharmaceutical industry? Regulatory authorities have seen to it that companies engaging in drug research and development only play with blue chips. The smaller denomination of chips no longer goes. But what will happen to the drug company that is fortunate enough to hit the new drug jackpot? Will it be short-changed? Will it receive, say yellow chips for the blue chips it has put on the table? I feel the answer is blowing in the wind.

The answer is no longer given by the marketplace from where the answer should come. It is no longer given, to a large extent at least, by the doctors based on the experience they have with the individual drugs. The decision is given from one year to another to a larger extent by governments, who dictate in large parts of the world the prices of drugs. As an alternative to this, they manipulate the pharmaceutical market in a way that suits their convenience by going beyond safety, efficacy and quality aspects, when registering drugs, by controlling the use of drugs.

This trend towards government control of the pharmaceutical industry is quite aptly described in the draft of a UNIDO study of the pharmaceutical industry, and I would like to quote from it:

'Policy and decision makers (of the pharmaceutical industry) in the future will not be faced solely with the past tasks which centred around discovering, financing, producing and marketing ethical drugs under relatively laissez-faire conditions, but with a set of societal variables in a highly controlled environment largely determined by governments acting at the behest of and as the guardians of society.'

I pray for the sake of this very society that UNIDO refers to that the governments of tomorrow will exercise this authority, if and when they assume it, with caution, wisdom and foresight.

GENERAL DISCUSSION – SESSION I

At the start of the discussion several speakers, including Sir John Butterfield and Sir Douglas Black agreed with the view that medical and social aspects of health care are still poorly coordinated. The consequent friction between the social and medical services could reduce benefits for the sick.

Dr J. Parker then raised the question of whether technological innovation in medicine came in Butterfield's 'series of heroic steps' or whether it came as a series of small progressive steps. Parker felt that if the former model was accepted there was a danger that people would be persuaded 'to wait around for a genius to arrive'. His own studies had suggested that innovation in general tended to be a process typically involving minor improvements. In response, Butterfield did not disagree, but he felt that

there were nevertheless innovative 'giants' such as Fleming on whose shoulders others could stand.

As far as innovation in pharmaceuticals was concerned, there were again differences in points of view. Mr R. First (Robert S. First Inc, USA) felt that many important non-drug medical innovations such as kidney dialysis and cardiac pacemakers had come from the work of small entrepreneurs. On the other hand for pharmaceuticals, Professor D. R. Laurence (University College Hospital, Britain) said that, though he had heard the contrary stated, he thought most major developments had originated in large firms. He was not sure if that was chance or because enormous resources were now essential. He agreed with Mr M. Tiefenbacher that the industry needed assurance of appropriate returns for its investment in research and development if it was to undertake really original research. Professor D. Long (University of Sussex, Britain) emphasised the continued need for pharmaceutical innovation to overcome the problems of resistance to the current range of antibiotics. Professor R. F. L. Logan (London School of Hygiene and Tropical Medicine, Britain) pointed out the increasing importance of the elderly in health care terms; those over age 65 although accounting for just 13 per cent of the population use 48 per cent of acute hospital resources alone – once again underlining the need for well supported research.

Dr N. Olsen (British Medical Association, Britain) then raised the question of the efficacy of older medicines. Both Butterfield and Sir Eric Scowen (Chairman, Committee on Safety of Medicines, Britain) described the process of review for existing medicines at present in progress in Britain. The latter emphasised that the problem of less effective traditional medicines related more to those purchased without prescription rather than to those prescribed by doctors.

Dr W. P. von Wartburg (Ciba-Geigy, Switzerland) raised the question of risk-taking in medicine. The experience of his own company had been that patients were prepared to take a high degree of risk in relation to medicines. It was the government regulatory authorities rather than the patients themselves who were excessively worried about risks. He felt the authorities should have a greater concern to promote technological innovation. Butterfield agreed that the problem was one of getting the right sense of perspective.

The discussion then turned back to the question of proper returns for the risk of pharmaceutical research and development. Mr D. Moreau (Weddel Pharmaceuticals, Britain) felt that the problems associated with innovation in a small company were now such that they would be discouraged from undertaking research. The future of medicines for the year 2000 lay in the hands of the large multinational companies and the government regulatory agencies.

SESSION II

Present Problems (1)

Chairman *Mr G. J. Wilkins*

Within the framework of our Symposium title we are to discuss 'Present Problems' this afternoon and you have three very eminent speakers to present their views to you. The background of each one is known to you and in the case of many participants you will know the speakers personally so I shall not take up valuable discussion time with personal introductions.

The Chairman at such a session has very little to do other than see that the timetable is adhered to and that the proceedings, particularly the question and answer period are kept under control, and not allowed to get unruly. He also has the privilege of a few opening sentences and occupying the most comfortable chair.

I am sure that everyone would agree that we do have problems at present in the health care services – there might even be general agreement as to what they are but I suspect that there are significant differences of view as to their priority and how they should be solved.

I want to make two general points before the papers are read. One is that from the point of view of a businessman running a research-based pharmaceutical company, and a potential patient as we all are, the main problem is that the pharmaceutical industry suffers from too much intervention and regulation.

In my experience and I stress that this is my experience, all politicians are interventionist by nature. As a consequence most if not all government servants are also interventionist and produce and monitor regulations to serve their political masters.

It never fails to amaze me how politicians convince themselves that they know best, and can intervene into, and plan the economy and allocate resources and priorities better than 'market forces' can. What is worse they claim to be doing it for the benefit of the public. Since they usually know so little about any complex subject they usually get it wrong and the public suffers rather than benefits.

My other point is a plea for some de-regulation instead of continually increasing regulation – particularly where it becomes obvious that changes are required. I have reluctantly to accept that we can never get back to a completely free market system but I would ask those involved in drafting and enforcing regulations to be more forward looking and to take a broader view that takes into account more than the country in which they happen to be operating.

The regulation of drug prices

David Schwartzman
New School for Social Research, New York

Long before public policymakers were distressed by rapidly rising medical costs, they recognised that new drugs supplied cheaper and often more effective therapy than hospital care or other medical technologies, but thus far perversely they have tended to discourage rather than encourage drug innovation.

The goal of limiting monopoly power has received priority, and governments have controlled prices. In recent years administrators of social security systems which pay for the drugs have responded to the rising costs of medical care by strongly supporting efforts to keep prices low.

Those European governments that have refrained from controlling drug prices – Holland, West Germany and Switzerland – may not be able to continue to refuse to go along. In fact, the Common Market has spread the effect of price control by obliging countries to import drugs, thus reducing the prices of each drug in all member countries to the level of the country with the lowest price. The European Court of Justice, in a decision handed down in 1976, forced Holland to accept imports of low-price drugs from the United Kingdom, which were sold in Holland at prices that are 10 to 20 per cent lower than those of the same drugs from established sources. Although recent price increases in the United Kingdom have reduced such imports, they will continue to depress prices, especially since the European Economic Commission is determined to encourage the equalisation of prices. It promises to investigate 'dominant' companies practising 'abusive' pricing.[1]

One line of policy that the Dutch government, along with those of the United Kingdom and West Germany, has pursued deliberately is to reduce the prices of individual major drugs. Manufacturers fear that the Dutch government's ordering Hoffmann-La Roche to reduce the prices of two of its major products, Valium and Librium, is the first in a series of such actions. Apparently it becomes an offence when a drug attracts a dominant share of the sales in a therapeutic class. Price reduction orders directed against manufacturers of leading drugs are not in the public interest. Fortunately, companies compete by striving to discover and develop new drugs which are so much more effective and safer than their predecessors that they obtain a large share of the sales in a therapeutic class. Moreover, important discoveries are rare, so unless those which do emerge are allowed to earn large profits, the total return from investment in research will be depressed to a level which will discourage further investment. The Dutch government's sensitivity to the monopoly issue thus endangers the socially beneficial form of innovative product competition.

In West Germany the Cartel Office's orders to Hoffmann-La Roche and E. Merck, of Darmstadt, to reduce prices have been contested in the courts, resulting in a modification of the original orders. The issue has been before the Supreme Court once before, and the companies have

entered a second appeal. The future augurs badly for innovators, since the Court's decision has provided the Cartel Office with guidelines for future prosecutions. Thus, in Germany, as in other countries, the strongly rooted hostility towards high profits is expressed in a public policy discriminating against the most successful drugs.

The three nonconformist governments thus are not exempt from the concern over the monopoly issue, and they are leaning towards the European norm of price control. They may select the British system of profit control, which permits a manufacturer to adjust individual drug prices, provided the company's costs are reasonable and the rate of profit on the company's total United Kingdom ethical pharmaceutical sales remains at a level accepted as not excessive by the Department of Health and Social Security (DHSS). The unit of control in the British system thus is the firm. The three governments, on the other hand, may prefer the more *dirigiste* system adopted by most countries, requiring the control of individual drug prices. In this system the unit of control is the individual product.

We will investigate the effects of these price regulation systems on investment in R and D and on efficiency. We will avoid a tedious, comprehensive survey, from which little will be gained, by taking the French system as the example of individual drug-price control systems. We will also examine the British system. To evaluate the effect of price control in this industry, we need to understand the sources and degree of uncertainty of pharmaceutical research and also the goals of price controllers. We examine some aspects of pharmaceutical research first.

The uncertainty of investment in pharmaceutical R and D

Pharmacology still is too primitive to permit confident evaluation of the therapeutic prospects of a substance at an early stage of research. In this field, unlike physics, researchers cannot be certain of achieving their goals before the product has actually been used. By contrast, President Kennedy could set a ten-year deadline for landing a man on the moon, because only technological problems were left; the underlying theory was sufficiently complete for scientists to be confident of success. A disease, on the other hand, usually is little understood, even after effective drugs have been discovered. Necessarily, research consists of the trial-and-error pursuit of clues, furnished by the observation of biological effects of natural substances, or of chemicals, including previously known drugs. Whether or not a substance will be effective without inflicting serious side effects long remains uncertain. In fact, the decision to enter a field of research commits a company to employ a staff who will do little more for ten years or more than learn the special problems of that field. Further, technical success does not assure commercial success: the new drug may have no significant therapeutic advantages over its predecessors.

There is plenty of evidence of both technical and commercial uncertainty of pharmaceutical research. In 1970 in the United States 703,900 substances were pharmacologically tested compared to only 1,013 substances that were clinically tested, and only 16 new chemical entities reached the market that year.

Commercial uncertainty is evidenced by the fewness of new entities achieving large enough sales to earn an adequate return on the investment

in their research. I have estimated on the basis of costs of research in 1972 in the United States that a new chemical entity will earn over 10 per cent after taxes on the investment in research only if annual world sales exceed $23.5 million. Of the 79 new chemical entities introduced in the United States between 1962 and 1968 only 8 sold well enough to earn this rate of profit. Despite large research expenditures many companies failed to introduce a single new entity meeting this standard. The sales of 33 of the 79 were less than $1 million; a majority obtained sales of less than $2 million.[2]

Under these conditions the expected rate of return from investment in research must be above that from alternative investments in order for investment to be maintained. But the expected return from investment in pharmaceutical research is low by any standard. My study estimated the average expected after-tax rate of return to be only 3.3 per cent.[3] Although this estimate is based only on the costs of research and on world sales of United States manufacturers, companies based in other countries probably do no better. The advantage of lower research costs in Europe owing to less restrictive regulation of research may be offset by smaller home markets and by price regulation.

It should be noted that any firm contemplating investment in research will evaluate the expected rate of return on the basis of the industry's experience. Regardless of the firm's own innovational record, it can expect its own investment to yield a return equal to that of the average for the industry as a whole. A firm will improve a poor staff, and a firm will find it expensive to keep a good staff intact. A run of bad luck will end as will a run of good luck.

Since the expected rate is inadequate rather than excessive, there is no need for price control. The last time the expected rate was above 10 per cent, which is a conservative benchmark for so uncertain a field as pharmaceutical research, was about 1960, following a period of unusually productive research.

The impression of monopoly power is promoted by the record of high realised profits, which may be due to many things. My own analysis of the difference between the average realised profit rate of the United States industry and that of all manufacturing revealed that the difference can be accounted for by the accounting method of expensing research costs, the riskiness of investment, and the growth of demand. The difference between the average realised rate of profit on equity for the United States industry, 18.1 per cent, and that for manufacturing as a whole, 10.6 per cent, in the period 1968–72, was 7.5 percentage points. Applying the economically appropriate method of measuring the profit rate, which capitalises R and D expenditures instead of treating them as current expenses, reduces the difference by 3.5 percentage points. Risk accounts for an additional 2.8 percentage points, and the growth in demand for 1.1, leaving a final nonsignificant residual of 0.1 percentage points, not enough to indicate monopoly power.[4]

Further, the expected rate of return is a better locator of monopoly power than the realised rate. The expected rate reflects current prices and costs, while the realised rate reflects those of the past. The prices of new drugs thus are not monopolistic.

We turn now to some characteristics of price regulation systems.

The administration of price regulation

Although regulators will pursue other goals, such as industrial development, the primary one is to reduce the cost of drugs to national or other insurance systems. This goal turns regulators and sellers into adversaries. This fundamental aspect of drug price regulation is often obscured by advocates of regulation who assert that regulators serve national economic goals. So general a statement is meaningless without the specification of priorities. Given the primary objective, regulators will seek to reduce drug prices. Although the overall objective of a health care system which is to provide such care at a reasonable cost might allow manufacturers sufficiently high profits to encourage research, price regulators have sought to reduce the cost of drugs. The policy is a response to pressures from administrators of insurance systems and to the widespread hostility to the apparent high profits of drug companies.

The regulators try to get the lowest prices possible. Since they negotiate with many sellers, becoming involved in details of costs of manufacturing, prices of competitive drugs, and costs of materials, they try both to simplify negotiations and to save time. Rule number one, therefore, requires precise, simple, nondiscriminatory, and nondiscretionary formulas. Further, since regulators can either inflict losses on sellers or confer benefits, rule number two is that prices must be fair, meaning that they must be based on costs, the prevalent standard since the middle ages. A price regulator's duty is to reduce high profits. The principles thus directly undermine the disciplinary function of the market, that of rewarding efficiency, and they reduce investment incentives, especially where the success of investment is highly uncertain, as in the case of pharmaceutical research.

Price controls also provide a handy instrument for advancing a variety of goals, further contributing to the destruction of market discipline. Both French and British statements of objectives of price control include the encouragement of exports among the objectives, and there may be other secondary objectives.

Finally, while the standard for price control is the realised profits of individual firms, the relevant criterion for economic policy is the expected rate of return from investment which must be estimated for the industry. It is difficult to regulate the expected rate of return. It can be estimated, and changes in policy to increase or reduce the expected rate may be proposed, but the expected rate does not lend itself to direct control. In addition, the accounting tradition of measuring a company's performance according to its realised profits dominates any analysis of profits. Even economists are misled by this tradition and tend to view the investment prospects of a company as favourable when realised profits have been high. In this industry the view is inappropriate not only because of the high degree of uncertainty associated with investment but also because of the long period required for investment in research to generate profits. The tradition also dominates discussions of monopoly profits; high realised profits for individual products or firms are taken to be evidence of monopoly power. Again in this industry such data on profits are likely to be misleading.

Drug price regulation in France

Brief summary of the history of regulation

The French drug price control system from the outset in 1945 was based on estimates of direct costs. Direct costs are less discretionary than general and administrative expenditures, which executives may inflate by paying themselves higher salaries. Another virtue of direct costs as a standard is that unless they are covered, production will soon cease, while failure to cover other costs has more delayed effects. In addition, the problem of allocating direct costs among different products is less serious than that of allocating overhead and other costs.

Accordingly, in 1945 the government adopted the following price formula for each new drug registered as reimbursable by social security:

$$P = \frac{D}{1 - a}$$

where P=price, D=estimated direct manufacturing cost for the drug, and a=the margin for general and administrative costs, research and development, selling costs, and profits. To estimate *D* required an allocation of direct costs, including the cost of materials and packaging, wages in the plant, power, and fuel among individual products. By contrast, *a* was based on the proportion of sales represented by non-direct costs in the entire company in the previous year. If direct costs in the company as a whole amounted to 30 per cent of total sales, then *a* was set equal to 0.7 for each new product. The reasonableness of *a* for a particular company was checked by comparing its value with those of other companies.

The revisions implemented in 1968 codified practices established in earlier years. The revisions broke *a* down into its components: general and administrative expenses, selling costs, research and development, and profits. Each of the cost components was estimated on the basis of its share of total company sales. The average research and development costs for the industry was set at between 7 and 9 per cent of total sales, but individual companies received larger allowances. Regulators negotiated the profit allowance with each company.

The new regulations of October, 1977, again are largely a codification of practices developed earlier. They retain the direct-cost formula embodied in a *grille de prix* for those new drugs that the Coudurier Commission judges to be innovative. Even the apparent change in the pricing of new drugs that are therapeutically similar to older ones is only an official recognition of actual practice. No *grille de prix* is constructed. Instead, the Commission attempts to simulate a competitive market by setting the price of a non-innovative new drug at a lower level than the weighted average of the prices of its predecessors in the same therapeutic class, which it defines. The procedure requires less work than constructing a *grille de prix*, since it is easier to compare the prices of a limited number of drugs than to estimate costs.

The most significant change is to establish a procedure for supporting ambitious research programs. A company seeking a large margin must obtain approval for the program from a committee representing several ministries before the Coudurier Commission can allow price increases.

The goal, according to the Ministers' statement describing the new regulations, is a domestic pharmaceutical research capability, thus excluding foreign research from equivalent treatment.

The Ministers' statement refers to the frequently difficult problem of evaluating transfer prices charged to domestic affiliates of foreign suppliers. Differences among multinational corporations in the allocation of profits between home and host countries complicate the problem. The Commission, therefore, estimates the manufacturing costs of imported bulk materials from a variety of data sources. The figures finally used often are negotiated, because the Commission's estimates are not precise, and some allowance may be granted for foreign research. The Ministers' statement does no more than call for the collection of more data on prices of materials.

The effect of regulation on prices and costs

The price formula breeds inefficiency by promising to cover direct costs and thus tends to raise rather than lower prices. Perversely inefficiency yields higher profits; any addition to direct costs adds to the price, and since the profit is calculated as a percentage of sales, it rises with the price. Manufacturing inefficiency also inflates general and administrative costs, the R and D allowance, and selling costs. The inflationary effect is larger in the pharmaceutical industry where direct costs account for a relatively small part of total costs than other industries.

Why then are prices lower in France than in Germany or the United Kingdom? The evidence that French prices are lower is strong enough to withstand doubts concerning the validity of international price comparisons. We postpone the consideration of the reasons for the relatively low prices in France until after we review the evidence of Michael Cooper's international comparison (Table 1).

Although the results of the study reported in Table 1 refer only to 1974 and reflect one set of weights, the conclusion that prices in France have been lower than those in Germany or the United Kingdom is also reached with data for other years and other weights. Table 1 also shows that French regulators have been more severe than those in Italy and Belgium, where they also use a direct-cost formula.

Cooper refutes the objection that fluctuating exchange rates invalidate international price comparisons by computing indexes for each year and applying the exchange rates of different years. Prices in France are shown

TABLE 1 **Index of average price per unit of drugs weighted by United Kingdom sales, 1974**

United Kingdom	100
France	88
Germany	221
Italy	127
Belgium	120

Source Michael Cooper. *European Pharmaceutical Prices* 1964–74. London: Croom Helm, p 4.

to have been below those in Germany in 1964, 1969, and 1974 regardless of whether the comparisons are based on exchange rates of the same year or of other years. In general, prices in France also were below those in the United Kingdom, Italy, and Belgium.[5]

Cooper's study thus proves that the Coudurier Commission has kept prices below those in Germany and the United Kingdom. Our hypothesis that the direct-cost formula inflates prices is not confirmed, because the French government issued various orders which cancelled this effect.

Returning to our question, first and most important, rigid price controls have been maintained in the period of general inflation. Although manufacturers sought to keep up with increases in costs by withdrawing old drugs and by introducing new preparations, which allowed them to submit a new *grille de prix*, reflecting current costs, the rigidity of prices of the remaining old drugs depressed the average price. The Commission could not indefinitely keep the prices of old drugs from reflecting increases in costs, and beginning in 1976 it permitted increases in these prices. (This history suggests that the inflationary effect of the formula will be enhanced by the frequent price adjustments called for by the new regulations.)

Second, the prices of large-selling drugs have been reduced from time to time. For example, in 1976 prices of 250 leading drugs were reduced by amounts varying from 1 to 7 per cent.

Third, regulatory strictness has reduced prices. The Commission has refused to accept a company's estimate of the price of a material purchased from a foreign affiliate in the face of lower prices in other countries. The Commission also has challenged firms' administrative and other margins when they have exceeded other sellers' margins, producing a downward bias in cost estimates. The Commission has not offset this bias by challenging low margins.

Fourth, the Commission has applied the standard of prices of similar drugs, when it has judged this standard to be appropriate. Comparisons with the controlled prices of old drugs within each therapeutic class have depressed the prices of new drugs.

The severity of price regulation has discouraged pharmaceutical research, despite the research allowance in the *grille de prix*. Companies have no incentive to seek a major discovery, which will not raise profits substantially. The policy simply recompenses and therefore induces expenditures up to the limit of the allowance regardless of the objectives of the research, thus accelerating the development of new formulations and imitations rather than significant therapeutic advances.

The regulators also have reduced margins for general and administrative expenses and for selling. Reducing expenditures for planning, administration and purchasing probably has increased costs of production. Even greater distrust has persuaded regulators to limit selling costs. The uninformative attention-getting content of much of advertising and the argument that monopolistic conditions raise selling costs have provoked this policy. But in this industry the need for much information about many products by many physicians is the major source of high selling costs. The selling of drugs resembles the selling of such technical products as hospital equipment, dental supplies, and office machines. Patients' benefits from information to doctors can easily outweigh the costs.

The new regulations and the prices of therapeutically similar drugs

Although government reports have pointed to problems in price regulation, none has dared to challenge social security administrators by recommending its abandonment. Since even details of the system, such as the use of a *grille de prix*, are difficult to dislodge, the new (1977) regulations retain much of the old system.

As we have seen, the new regulations require non-innovative new drugs in any therapeutic class, as defined by the Commission, to be introduced at successively lower prices, and persistent price disparities will be removed by suitable price adjustments. Some of the work saved by eliminating the estimation of costs is reintroduced by requiring estimates for the harmonisation of prices. Probably regulators will estimate the costs of a sample of firms manufacturing each group of similar products.

The new regulations also call for annual price changes, because the price controls encouraged the replacement of useful old drugs, which were priced when costs were much lower, by new but not better drugs which can be sold at higher prices. The Commission attempted to discourage the introduction of imitations, but the Ministers' call for newly constructed therapeutic classes suggests incomplete success. The Commission also will permit price changes for groups of drugs classified by age and therapeutic class to reflect cost changes.

Nevertheless past price regulation will continue to depress prices. The price adjustments are to be based on recent costs, but these costs reflect past expenditures restrained by regulated prices. It will be difficult to estimate the appropriate prospective costs. The Commission cannot have enough information for correct estimates of the appropriate costs for each firm, and it cannot attempt to do so without usurping the management of the firms.

The new regulations and the prices of innovative new drugs

The Commission will estimate a *grille de prix* for breakthrough drugs. A major change in the estimation is in the handling of selling costs.

Under the old formula increases in direct costs tended to raise selling costs, since a fixed proportion of sales was allowed for this item. But the new standard calling for a fixed absolute allowance per unit of output is equally absurd, for firms are allowed larger expenditures for widely known products than for useful but unknown products.

The government will continue to wander from one device to another. No simple formula can be fair and provide for varying informational demands. The informational purpose cannot be satisfied without entrusting regulators with a great deal of authority. Regulators would have to duplicate the activities of marketing managers. The marketing manager is primarily concerned with sales rather than information, but it comes to the same thing. He estimates the sales elasticity of promotional expenditures for a particular drug by considering its market share, which is an index of how widely known the drug is, given its therapeutic merits. Expenditures for an unknown, but superior drug will tend to be large. To decide the appropriate amount of advertising a regulator would have to repeat this market analysis. How can a regulator dare to assume the marketing manager's role for different competitors?

Another change is the provision for changes in the prices of innovative new drugs after two years of marketing. Since the *grille de prix*, of course, consists of forecasts rather than estimates of actual costs and output, the change may appear to be sensible, something which should have come sooner. But it turns out to be a method of reducing profits arising from uncertainty. Consider the likely forecasting errors. Since the prices of materials, wage rates, and the technology are known in advance, the major uncertainty pertains to sales. When an excess of actual over forecast sales results in excess profits, regulators will reduce prices. Thus market success will increase profits much less than before. Profits will be less important in directing resources and in rewarding skill, good judgment, and risk aversion.

Such a system would be unsatisfactory even in the relative certainty of a public utility setting. Regulated public utilities take the trouble to make correct decisions, to refuse demands for wage increases, and to bargain over coal prices only because they can increase their profits in the interval between changes in rates. The provision is especially harmful to performance where success is highly uncertain, as in pharmaceuticals.

Basically the requirement of a change in the price of a new innovative drug two years after marketing expresses the suspicion that large sales and the resulting high profits reflect monopoly power. The policymakers continue to ignore the fact that the probability of a commercially successful discovery is very small. The high profits from individual, successful products should be set against the losses from the large number of failures in the industry as a whole. The appropriate unit for analysis is neither the single product nor the firm, but the industry as a whole.

The French government can reduce prices without suffering serious consequences, because France is a small part of the world market. This is an instance of the general problem of the conflict of interest between the community as a whole and part of it. France can continue to exploit the gains from pharmaceutical research in the rest of the world so long as other countries refrain from pursuing similar policies. Unfortunately, as we have seen, other countries are moving in the same direction.

The new regulations and research

The new regulations allow the social security system to support ambitious domestic research programs by paying higher prices for sponsoring companies' products both new and old. The Ministers try to protect the public purse by requiring approval for each program from a special interministerial committee before the Coudurier Commission grants price increases. The question is: How can the interministerial committee, appropriately nicknamed 'the four wise men', select the most promising programs?

Even with the assistance of experts, the Committee will be unable to evaluate research programs. As I said earlier, pharmacology is too primitive to permit good predictions of the outcome of a research program. The Committee is being asked to do what manufacturers themselves cannot do. In effect, the Committee is to award research contracts to manufacturers, something which manufacturers themselves do not risk because the success of research programs is difficult to predict. A manufacturer will not award a contract without a good estimate of the probability of success

and a ceiling on the costs, and an independent laboratory cannot undertake to discover a drug without a guarantee that its costs will be covered. Operating their own research laboratories does not assure manufacturers of success, but it does permit them to supervise and thus to evaluate the performance of the laboratories. For this reason contract work includes only routine jobs for which prices can be quoted, as for example, standard animal tests. The manufacturer's laboratory staff thus must specialise in the fields of research related to a proposed drug in order to be able to design, perform, and evaluate tests for efficacy and side effects. A government committee will have similar problems in evaluating the work of laboratories.

There are other problems. How long will the Committee wait for new drugs before it discontinues support? Will it require periodic reports? Will the Committee limit its support to companies having the necessary facilities and staff? If it does, it exposes itself to the accusation of discriminating in favour of Big Business.

What is likely to happen? The government probably will support research at a few favoured laboratories, only some of which will be productive. Uncertainty will make it difficult to evaluate the competence of the laboratories. Therefore, companies will have no incentive to control costs; the supported companies will not be spending their own money. Policymakers mistakenly have regarded research as a routine activity, imposing no greater problem of efficiency assessment than the production of Renaults. Thus the price-control system paradoxically will raise costs rather than reduce them.

The responsibility for pharmaceutical research thus is best left to the manufacturers, who will choose the projects, supply the funds, perform the research, and take the risks. Successful manufacturers will earn profits; the others will not. Since the risks and the responsibility for the direction are undertaken simultaneously by the same unit, the cost to the economy of the risks is minimised.

The British system of price regulation

The United Kingdom's Pharmaceutical Price Regulation Scheme (PPRS) is more flexible and easier to administer than the French system, because it controls only the total profits of each company, leaving manufacturers free to set their own prices. The unit of control is the firm rather than the product. A manufacturer may meet competition by cutting the prices of some drugs, while maintaining the prices of other drugs. The profit-control system also has the advantage of requiring less haggling over estimates of direct costs of individual products and over prices.

My basic objection to the profit-control approach is to its reliance on the usual accounting estimates of capital and of rates of return. The expected rate of return from investment has no place; high profits from past success trigger price cuts regardless of the prospects for new entities. In addition, of course, the DHSS looks at the profits of each company rather than at the economically appropriate unit, the industry.

Another major problem with this system is that it distorts the incentives for research by accepting the public-utility model of price control. Why should a manufacturer improve efficiency or push its scientists to discover

a drug which will not raise profits? The frequency of reviews makes matters worse. The annual reviews are intended to keep the intervals between price changes from being long enough to permit profits to increase significantly. What is more, the DHSS is so vigilant that it demanded early reports when profits were expected to be high.

In relation to promotional expenditure, the DHSS substitutes its own judgment for market discipline, probably not very successfully. Objections can easily be found to the DHSS's rule-of-thumb ratio of promotion expenditures to sales. How much should be allowed for new drugs? How long does a drug remain new? How much more per dollar of sales should be allowed small firms than large ones? A small difference will inhibit growth, but should the public pay higher prices to finance the growth of small companies?

The system, moreover, is not as simple as it appears to be. Like the French Coudurier Commission, the Department cannot avoid evaluating transfer prices when the domestic affiliate of a multinational enterprise reports lower than expected earnings. Finally, the system allows companies less discretion in pricing than is claimed, since usually only a handful of drugs furnish most of a company's sales.

Some of the problems raised by the approach are illustrated by the report on Librium and Valium which the Monopolies Commission issued when the government assigned to it the task of determing fair prices for those products. Although monopoly power was the issue, the Commission did not compare the prices of the two drugs with those of older tranquilisers. Without any justification, the Commission's case against Hoffmann-La Roche rested instead on the estimated size of the excess of prices over costs.[6] The Commission estimated the cost of manufacturing the bulk materials which the British affiliate of Roche imported from Switzerland from prices in Italy. The Commission also estimated Roche's research expenditures throughout the world and other 'Group', as opposed to local costs, allocating to the British market what it considered to be a fair share. The Report, which did not mention the uncertainty of pharmaceutical research, attributed the high estimated profits to monopoly power rather than to exceptional skill or luck. The Commission therefore recommended substantial price reductions. The Report arrived at this recommendation without inquiring into the nature of competition in the industry, contrary to one's expectations of the Monopolies Commission.

The appeal of the doctrine that no firm is entitled to more than a reasonable profit is so overwhelming that the writers of the Report appear to be blinded to the possibility of variation in the rate of profit among firms in an industry. An essential feature of competition in this industry appears not to have crossed the minds of the writers. They have failed to recognise that profits in an unregulated, competitive industry might vary greatly among firms with the number and importance of drug discoveries. Perhaps the failure to consider the issues posed by this characteristic of competition in the industry is due to the problem of reconciling it with the demands of regulation, ie, with the objective of regulating profits.

Why then is the performance of the British industry as good as it is? Firms continue to seek important new drugs, and their scientists are as productive as any. The puzzle is solved when one realises that the DHSS

regulates only the domestic sales market and not exports, accounting for about half of total sales; regulation has reduced but not destroyed the market incentives. The British can thank the world market for keeping their industry healthy.

Sources of competition

The obvious reply to the monopoly argument in defence of price regulation is that the industry is competitive, society benefits from product competition in this industry, and society would lose if more active price competition were to replace product competition. If new products could not earn higher profits than therapeutically inferior older products, there would be no incentive to invest in research. Nevertheless, this argument is not entirely persuasive. Even innovators should not be granted monopoly power indefinitely, and prices may not decline to competitive levels after a patent expires without government control of prices. These considerations indicate a useful breakdown of products into two categories: single-source and multiple-source drugs.

There is some price competition even in single-source drug markets. Duncan Reekie's studies demonstrate competition in single-source drug pricing both in the United Kingdom and the United States.[7] A manufacturer must price a new drug that is not much better than its predecessors offering similar therapy at a level which is about the same or lower than those of its competitors, as measured by daily dosage cost, in order to achieve adequate sales. A manufacturer can obtain adequate sales with a relatively high price only when it introduces a clearly superior drug. The best drugs for the money win large market shares. The surveys indicating that some prescribers are ignorant of prices has little bearing on the question. The number of prescribers who are sensitive to prices need not be large to affect pricing decisions. Price affects the quantity sold even in the United Kingdom despite high reimbursements. Enough prescribers respond to information about prices and to pressures from the NHS for the price elasticity of demand to influence manufacturers' policies. Drug companies thus have set prices of new products at the same or below the level of competitive products except when they have clear evidence of therapeutic advantages.

In the United States price competition in multiple-source drugs has been very vigorous. Imitations entering after a patent expires are priced lower than the original drug, and their market shares grow rapidly until the original drug's manufacturer makes matching price cuts. Thus, as the patents for tetracycline, ampicillin, erythromycin, and penicillin VK expired or were challenged, major companies entered with imitations of the original drug at substantially lower prices.[8] Having no special therapeutic claims, the entrants had to cut prices to increase their sales. The entry of major producers with imitations encouraged physicians to prescribe generically – generic prescriptions grew to 40 per cent of multiple-source antibiotic prescriptions – or to prescribe low-price branded generics. Pharmacists filled a large proportion of generic prescriptions with low-price generics. In addition, pharmacists were substituting low-price generic drugs for original drugs specified in prescriptions even before the recent repeals of antisubstitution laws by many states. The market shares

of imitations therefore grew, forcing down the prices of original brands.

The use of generic drugs raises certain quality problems which cannot be passed over without discussion. In the United States as elsewhere there are many small manufacturers, employing only a handful of people, which find it difficult to observe the Food and Drug Administration's regulations governing good manufacturing practices (GMP).[9] Although the total output of these firms is small. there are so many small firms that the FDA has been unable to enforce its regulations, and for certain diseases the risk of poor quality drugs is unacceptably high. Generic prescribing and the substitution of low-price for high-price drugs stimulates price competition at the cost of increasing the risk of poor quality. The dilemma may be resolved by raising the GMP standards and the penalties for violations.

One of the reasons price competition is lively in multiple-source markets in the United States is that third-party payments are unimportant. Private insurance plans do not pay for drugs purchased from retail pharmacists and only the indigent are covered by a public plan – Medicaid. Doctors thus have an incentive to prescribe low-price brand name drugs or generically. Another reason is the price competition among retail pharmacists, who fill generic prescriptions with generic products and substitute low-price generic products for the prescribed brand-name drugs.

This analysis of the sources of price competition in the United States indicates that in France, third-party payments and retail price regulation have discouraged price competition. First, doctors will not take the trouble to prescribe generically when their patients pay only 10 per cent or 30 per cent of the cost of the drugs, the social security agency providing the remainder. Second, a fixed percentage retail margin based on the retail price makes it unprofitable to fill prescriptions with low-price drugs. Since the pharmacists' margin is one-third of the retail price, regardless of the price, the pharmacist earns more from expensive prescriptions than from cheap ones. Thus, generic prescribing might even raise average drug prices, since pharmacists would fill the generic prescriptions with the most expensive versions.

Conditions are somewhat more favourable to price competition in the United Kingdom. It is true that physicians are discouraged from prescribing either low-price brand-name drugs or generic drugs by the fact that their patients pay only 20p per prescription regardless of the price. However, when a physician does prescribe generically, the pharmacist has an incentive to fill the prescription with a low-price suitable preparation. When nonbranded versions are available the pharmacist's reimbursement is computed on the basis of the average wholesale price of these nonbranded products. If the pharmacist pays less than the average price, then he gains the difference. If a doctor generically prescribes a drug for which only brand-name drugs are available, then the reimbursement is no higher than that computed using the lowest price. The pharmacist stands to lose money when he uses more expensive products. These powerful incentives to use low-price drugs are effective only when doctors prescribe generically. The combination of DHSS publications comparing prices and the visits by Regional Medical Officers to doctors generating large prescription costs appears to have been effective.

Policy recommendations

The objective of encouraging innovation calls for the deregulation of the prices of single-source drugs and for governments to refrain from anti-trust actions against manufacturers whose only offence is to discover and develop a therapeutically superior drug which gains a large share of a therapeutic market. Controls over prices or other policies to reduce profits from the production and sale of single-source drugs should only be considered when the expected profit rate from investment in pharmaceutical research for the industry as a whole is persistently above some acceptable benchmark, and the high rate is not warranted by a string of drug discoveries. The expected rate has not been high since the early 1960s when it reflected the immediately preceding great period of innovation. The expected rate has not yet warranted controls of prices of single-source drugs.

We can expect more price competition in multiple-source drug markets in some countries. In Holland and in Germany the health insurance societies have been urging doctors with some success to prescribe cheaper drugs. The recent German law threatening financial penalties for doctors who increase their prescription costs more than the approved percentage applies pressure to doctors in that country. I have referred to the measures taken in the United Kingdom to reduce the costs of prescriptions.

The pressure on French doctors may be increased by eliminating or at least reducing the third-party payments for drugs. To win acceptance from the public for reducing government payments for drugs it may be necessary to compensate large drug users, such as the elderly, for the added cost of drugs. Payments for old age assistance might be increased.

Another recommendation is to encourage price competition among pharmacists by deregulating retail prices. In any case, the retail margin should not be a fixed percentage of the price.

A reduction in the share of total drug costs borne by the government and increased competition in the retail distribution of pharmaceuticals will promote generic prescribing and increase price competition at the manufacturer's level in multiple-source drug markets. The pricing of single-source drugs will also become more competitive, since doctors will be more inclined to consider price as well as therapeutic qualities in their choice of drugs.

An increase in generic prescribing will increase the risk of poor quality drugs being distributed. Government agencies charged with assuring drug quality may be forced to raise their standards of good manufacturing practice, the penalties for violation, and the amount of resources devoted to inspection. Unless these steps are taken, the added risk of poor quality drugs may not warrant the increase in price competition. The problem may already have arisen in Holland where there is a great deal of generic prescribing.

Pharmaceutical companies may protest against accelerating the introduction of generic products and promoting price competition on the ground that the revenue from the sale of original drugs supplies the funds for research. A large proportion of profits is devoted to financing research rather than paid out in dividends, and reducing profits will reduce the amount of research and therefore the rate of innovation. The amount of

research done depends not only on the expected rate of return from investment in research but also on the size of retained earnings. These considerations must be weighed in the evaluation of any proposed policies. It is difficult however to accept policies which preserve monopoly power indefinitely in order to permit the financing of research. It would be more sensible to increase the life of patents and to strengthen patent protection.

REFERENCES

1 *Official Journal of the European Communities*, No C98/8, 24 April 1978, Answer (16 March 1978) to Written Question No 916/77 by Mr Cointat to the Commission of the European Communities (22 December 1977).
2 David Schwartzman. *Innovation in the Pharmaceutical Industry*. Baltimore and London: Johns Hopkins University Press, 1976, pp 105–07, 146.
3 Schwartzman. pp 136–52.
4 Schwartzman. pp 155–60.
5 Michael Cooper. *European Pharmaceutical Prices* 1964–74. London: Croom Helm, p 4.
6 The Monopolies Commission. *Chlordiazepoxide and Diazepam*. London: HMSO, 1973.
7 Duncan Reekie. *Pricing New Pharmaceutical Products*. London: Croom Helm, 1977; 'Price and Quality Competition in the United States Drug Industry.' *Journal of Industrial Economics*, March 1978, vol 26, No 3, pp 223–37.
8 Schwartzman. pp 251–99.
9 Schwartzman. pp 226–50.

Regulation of the United States Pharmaceutical Industry: Current problems and policy developments

Henry G. Grabowski
Department of Economics, Duke University, United States

1 Introduction

This would seem to be a particularly appropriate time to consider the effects of United States regulatory policy on innovative new medicines to the year 2000.

Evidence has now accumulated from several studies that increased regulation has been one of the main factors contributing to slower rates of technological advance in pharmaceuticals over the past few decades. The symptoms of this decline in innovation in the United States case have been documented frequently – fewer new product introductions, declining overall shares of pharmaceutical prescriptions accounted for by new drug entities, higher R and D cost and longer development times for new drugs, fewer independent sources of R and D on new drugs, and an increased concentration of pharmaceutical innovation among larger firms. While increased regulation has not been the only factor underlying these adverse developments, studies involving international comparisons (eg the studies on drug lag) as well as other analytical approaches have pointed to more stringent regulation as an important factor contributing to declining pharmaceutical innovation.[1]

This is also an important time to reflect on the issue of regulation and innovation because there are a number of significant policy developments now under way that will have an important bearing on innovative medicines to the year 2000. The Drug Regulatory Reform Act, introduced into the Congress earlier this year, would result in a number of fundamental changes in the United States regulatory process. It is noteworthy that the preamble to this bill declares the encouragement of innovation and freedom of scientific inquiry as important objectives of regulatory policy. This is in marked contrast to all prior legislation on the regulation of pharmaceuticals. Nevertheless, despite these stated goals, the substance of the bill would significantly expand FDA controls over drug development and introductions and contains several other provisions that could plausibly operate to lower the returns from innovation. If adopted in its current form, it is hard to escape the conclusion that it would have the opposite effect on innovation from its stated objectives.

There are important policy developments now occurring in the market-

1 See, in particular, the discussion of these trends in Grabowski (1976, ch 2–4) as well as Wardell and Lasagna (1975) and Schwartzman (1976).

ing and distribution process for pharmaceuticals that also could have significant impacts on the future rate of innovation. These include the passage of substitution laws in various states, some of which now contain provisions that *mandate* pharmacists to substitute low cost generic products for prescribed brands (unless doctors explicitly prohibit substitution on prescription forms). Similarly, the Maximum Allowable Cost (MAC) programme is being developed to reimburse Medicare and Medicaid patients only for the prices of the lowest cost generally available product. Several of the provisions of the proposed new drug regulation law (eg the monograph system of licensing and the early release of safety and efficacy data) also are specifically designed to facilitate the entry of generic competitors. They thus would serve to complement these evolving cost containment policies at the state and federal level.

In assessing the probable effects of these new cost containment policies on the incentives for innovation, it is important to keep in mind that the average patent life for new pharmaceuticals is typically much shorter than the legal patent life of seventeen years. This is so because of the long gestation period that is now required to develop and gain regulatory approval for a new drug entity. As a consequence of this shortened patent life, the potential negative effect of generic drug substitution on the returns to innovation are significantly amplified. This issue will be analysed in further detail below.

In sum the combined thrust of current policy developments in the drug regulatory and marketing areas, although well intentioned and addressed to valid social goals, would appear to be clearly in the direction of reducing rather than improving the incentives to undertake pharmaceutical innovation. The rest of this paper will analyse this proposition in further detail. The next section presents some background material from recent studies of pharmaceutical innovation. The remaining sections then turn to current policy and specific analysis of the different provisions of the Drug Regulatory Reform Act and the drug substitution laws. The latter considers what changes in these measures appear desirable in order to expedite and encourage the development of innovative new medicines for the future.

II Recent studies of pharmaceutical innovation

A The benefits of innovation

Innovation in pharmaceuticals has special significance because of its central role in improving both the quality of human life and health. There are numerous examples, as several of the papers in this conference demonstrate, where new pharmacological agents have produced enormous therapeutic benefits in the treatment of particular illnesses. Deaths from poliomyelitis and whooping cough were virtually eliminated as a result of new vaccines introduced in the last few decades. Impressive declines in the death rate for several other categories also have been registered such as hypertensive heart disease, tuberculosis and meningitis as a result of new drug therapies. In addition, new pharmaceutical agents have resulted in a reduced need for hospitalisation and shorter hospital stays for many diseases.

A subsidiary benefit of technological innovation in pharmaceuticals that is often overlooked is that it provides a relatively low cost means of treat-

ing disease and producing good health. This is important because the health sector is characterised by scarce and expensive professional manpower, labour intensive activities and complex technical equipment – all contributing to a very high rate of cost inflation in health services over recent years. Where drug therapies have replaced other forms of treatment (as for example, in tuberculosis and polio), there have often been dramatic cost savings in addition to important health benefits.

The prices of pharmaceutical products have also exhibited a declining trend over time in real terms. This is in sharp contrast to most other health services. Over the last decade, 1967 to 1977, for example, the consumer price index for pharmaceuticals rose at an annual rate of 2.0 per cent compared to an annual increase of 6.1 per cent for the CPI for the same period. The important role of innovation in producing these dynamic declines in prescription prices has been demonstrated in recent studies by Douglas Cocks (1975) and Duncan Reekie (1978).

In sum, the rapid rate of innovation in pharmaceuticals has led historically both to important advances in therapeutic quality as well as a declining trend in the relative prices for pharmaceutical products.

B Declining rates of innovation and the drug lag phenomena

The discovery and development of new drug products has been the dominant form of competition in the pharmaceutical industry for the last several decades and private pharmaceutical firms have accounted for over 90 per cent of all new chemical entities (NCES) introduced into the United States since 1950. However, as discussed in the introduction, there has been a dramatically slower rate of new drug product introduction over the recent years compared with the early post-war period. In particular, the average annual rate of NCES introduced is now less than one-third the rate experienced in the early sixties. A number of studies by economists and others have examined the reason for this decline. They all have found the more stringent United States regulatory climate emanating from the 1962 Amendments is one major determinant factor of this decline in pharmaceutical innovation.[2]

The FDA has vigorously disputed this set of findings. In particular, it has argued that the dominant factors leading to a slower rate of new pharmaceutical introductions has not been increased regulation, but reflect more basic changes in scientific opportunities, more sophisticated and costly techniques for uncovering drug toxicology, increased societal awareness of product liability, etc.[3] As evidence to support this view, FDA officials have pointed to the fact that other developed countries with much less stringent regulatory systems also have experienced significant declines in NCE introductions.

However, international comparative analysis in fact strongly supports

2 See the discussion of this question in Grabowski (1976, ch 2) as well as in the more recent study by Grabowski, Vernon and Thomas (1978) and the references cited therein.

3 See the reference to former FDA Commissioner Schmidt's comments along these lines in Grabowski (1976, pp 17–25). More recently, the current FDA Commissioner, Donald Kennedy (1978) in his article 'A calm look at the drug lag' published in the *Journal of the American Medical Association*, has made similar claims. See, however, the response by Wardell (1978) also published in *JAMA*.

the hypothesis that regulation has been an important factor influencing the rate and timing of NCE introductions. Professor William Wardell's pioneering comparative analysis of drug introductions in the United States and United Kingdom over the first decade after the 1962 Amendments demonstrated that there were roughly 50 per cent more NCEs introduced into the United Kingdom than the United States. In addition, for the class of drugs that became mutually available in both countries, more than twice as many were introduced first in the United Kingdom. In a follow-up analysis of subsequent time periods, Wardell (1978) has found some narrowing of this drug lag since 1972 as regulatory differences between the two countries have narrowed.

Another basic objection that FDA officials have consistently raised to the analysis of drug lag and related studies of regulation and innovation has been the use of NCE introductions as the basic measure of technological advance. In particular, they have argued that what is important is not the total number of new pharmaceuticals available but the *quality* of the NCEs that do become available.[4] I have attempted to analyse this quality issue in a recently completed study of the international diffusion of drug therapies. While there are no commonly accepted measures of drug quality in the literature, I have examined various quality measures including ones previously advanced by the FDA in congressional testimony in 1974.

Some summary results of this investigation are presented in Table 1. This table shows that even if one focuses exclusively on the sets of NCEs introduced in the United States since 1963 that were explicitly classified by the FDA in 1974 as *important therapeutic gains*, the majority of them become available first in the United Kingdom. The trend in these data is especially significant. Over the initial five-year period 1963–67, the number of NCE's classified as important gains introduced first into the United States exceeded those for the United Kingdom by a wide margin. But over the most recent period for which data on FDA rankings were available, 1967–73, ten of the seventeen NCEs rated as important gains were introduced first in the United Kingdom, three were introduced here and abroad in the same year, and only three were introduced in the United States first.

Some of the reasons for this dramatic shift in behaviour over time are discussed in my paper on international diffusion. In particular, this change appears to reflect first, a lagged adjustment process of United States firms in their foreign introductions to the increasing regulatory conditions evolving after 1962; and second, the fact that, by the second period, foreign discovered drugs accounted for an increased percentage of the drugs classified as important gains. These trends shown in Table 1 for significant drugs may have moderated or changed since 1973, however, as regulatory process in the United Kingdom (and elsewhere in Europe) has become more stringent and United States policy toward the acceptance of foreign clinical data has become more lenient in character.

A comparative analysis of trends in R and D costs per NCE in the United States and United Kingdom in the decade after the 1962 Amendments by

4 For example, Kennedy, *ibid*, p 423.

TABLE 1 **Comparison of NCE introduction dates for United States and United Kingdom**

	Number (per cent) in UK				
	Total NCEs	*Before US*	*Same year*	*After US*	*Not introduced in UK*
Sample					
1 All NCE introductions in United States classified as Important Therapeutic Advances by FDA for the periods:					
a) 1963–67	24	7	5	10	2
	(100)	(29)	(21)	(42)	(8)
b) 1968–73	17	10	3	3	1
	(100)	(59)	(18)	(18)	(6)
2 All NCE introductions in United States for the periods:					
a) 1963–67	76	30	12	21	13
	(100)	(39)	(16)	(28)	(17)
b) 1968–73	66	31	10	11	14
	(100)	(46)	(15)	(16)	(22)

Notes and data sources

(a) Information on NCE introductions in the United States and United Kingdom were obtained from data compiled by Paul de Haen, Inc, and also from data supplied from Professor William Wardell which he obtained through questionnaire surveys; new salts or esters of previously marketed products are omitted;

(b) FDA classification of NCEs as Important Therapeutic Gain taken from data appendix to FDA Commissioner Schmidt testimony before United States Senate Sub-Committee on Health ('Kennedy Hearings'), 16 August 1974.

(c) Three entities classified as important gains by FDA (Softconbandage lens in 1973, Methylmetharcrylate in 1971, and mafenide acetate in 1970) were omitted from our sample because these entities are not considered NCEs in de Haen or Wardell listings and no entry dates for United Kingdom were obtained.

John Vernon, Lacy Thomas and myself (1978) also suggests that increased regulation has had significant effects on the costs of introducing new drugs as well as its timing of their introduction.

C The costs and returns to pharmaceutical R and D

A number of studies by economists have also been addressed to the costs and returns from pharmaceutical R and D.

A recent study by Ronald Hansen (1977) has analysed the average costs of developing and introducing an NCE into the United States using data from a representative sample of drugs investigated over the period 1963–75. He found that after adjusting for both costs spent on unsuccessful drug candidates as well as the time cost of money, the average cost of introducing an NCE, in 1976 dollars, was over fifty million dollars. This number reflects both the very high attrition rate in new drug candidates (less than one drug in ten clinically investigated becomes a marketed NCE) and the long gestation time necessary to develop and gain regulatory approval for an NCE (between seven and ten years).

David Schwartzman (1976) has used data on the sales of all NCEs introduced in the period 1966 to 1972 together with aggregate R and D expenditures for the industry to estimate an expected rate of return on R and D. His analysis indicated an after tax rate of return on R and D for this period of between 3.3 and 7.5 per cent, depending on what assumptions are made about the size of gross margins and product life. While these parameters may be increasing over time and achieve higher levels than past NCEs because of the fewer NCE's now entering the market, even Schwartzman's upper bound estimates would indicate relatively low returns on R and D for investments of this riskiness.

This general conclusion is also reinforced in data examined in a new study by Virts (1978). He compares Hansen's average R and D cost estimates for NCE introductions against the realised sales from all NCEs introduced over the period 1967–76. This comparison points up the extreme skewness of the rate of return distribution to R and D. While there have been a few big winners over this period, the data indicate that most drugs have failed to accomplish a real before tax return of 8 per cent.

In sum, these analyses of the costs and revenues from R and D, although subject to a number of individual assumptions and qualifications, all point to a significant decline in the realised rate of return on pharmaceutical R and D over recent periods. This finding is also consistent with aggregate trends in industry R and D outlays and the declining shares of the ethical drug market accounted for by new drug introductions.[5]

D The response of pharmaceutical firms

Elsewhere I have examined some of the effects these developments are having on the behaviour of firms and the structure of the pharmaceutical industry.[6] I shall only highlight some of the main trends here.

First, it is clear that many firms, particularly smaller firms, that developed and introduced NCEs in prior decades are no longer seriously engaged in the business of pharmaceutical innovation. This is reflected in the fact that the number of independent firms having NCEs has declined sharply since the fifties. Furthermore, an analysis undertaken by John Vernon and myself (1977) found a steadily increasing concentration of innovational outputs over the period 1957 to 1971. Furthermore, the percentage of NCE introductions and new product sales accounted for by the largest firms also rose sharply over this period.

Second, while the larger established firms continue to engage in competition through innovation, they have adopted a 'mixed strategy' response to the above trends. In particular, they have maintained their R and D activity in pharmaceuticals at relatively stable levels in real dollar terms, while simultaneously increasing their degree of diversification across other industrial activities.[7] Furthermore, firms have opted to perform a greater percentage of their R and D in foreign countries, consis-

5 For an analysis of these trends, see, for example, Grabowski, Vernon and Thomas (1978), Section I.

6 Grabowski (1976), ch 3–4.

7 An analysis of changes in diversification using SEC 10K data for the period 1973–77 is presented in Virts (1978). Analysis of trends in R and D outlays are presented in Grabowski (1976) as well as in Caglarcan, Faust and Schnee (1976).

tent with the greater percentage of revenues from foreign markets and also the possibility of incurring less stringent regulatory controls in early clinical investigations of new products. R and D managers have also indicated that significant shifts in the character of R and D are occurring. Greater emphasis is now being put on drugs with large therapeutic markets and where the risks of regulatory problems can be minimised.[8]

Innovation competition in the pharmaceutical industry therefore has entered an uncertain period. Overall, firms are generally maintaining but not expanding their pharmaceutical R and D activities, while seeking out a number of ways to cope with a less favourable environment for innovation. Whether this approach will be successful remains open to question however. As noted at the outset of the paper, current policy developments now appear likely to generate greater rather than less pressure on the economic returns to R and D in the immediate future. The remainder of this paper is devoted to an analysis of these developments.

III Current policy developments in drug marketing and distribution

A Introduction of state substitution laws and the MAC programme

As discussed in the introduction to the paper, there are important institutional changes currently occurring in the marketing and distribution process for ethical drugs. First, the MAC programme under development by HEW is designed to reimburse Medicare and Medicaid patients only for the lowest cost commonly available generic drug products. Second, the majority of the states in the United States have repealed their anti-substitution laws which prohibited pharmacists from substituting generic equivalents for particular brand name products when prescribed by physicians. The present analysis will focus specifically on the effects of the substitution laws on the incentives for pharmaceutical innovation, in part because they potentially affect a much greater fraction of total pharmaceutical prescriptions. However, the two programmes clearly have qualitatively similiar effects and implications for innovation.

Until quite recently, virtually all states of the United States had anti-substitution laws. However, by the end of 1977, thirty-one states had passed substitution laws with a wide variety of different characteristics. All such laws essentially convey the rights to pharmacists to substitute generic products for brand names unless physicians take some specific action to prevent this from happening (eg, write dispense as written, check or initial a pre-printed box on the prescription, etc). Moreover, in five states (Florida, Kentucky, New York, Pennsylvania and New Jersey), the laws have been written or amended to *require* pharmacists to substitute lower cost drug in stock unless physicians specify substitution is not permitted.

Since substitution laws have been in existence at most only a few years, the market response to them is still evolving and it is not possible yet to predict what their full impact will be. Over the initial period, however, the actual amount of substitution has been relatively modest and the overall

8 See Grabowski (1976), pp 44–54, for a discussion of these developments.

level of saving to consumers has fallen far short of policymakers' expectations.[9] Several reasons have been cited for this general result. These include concern by pharmacists and patients about possible quality differences in different manufacturers' products, lack of very good information by consumer about savings from generics, and possible liability problems for pharmacists who do substitute and a toxic reaction occurs.

In interpreting these early experiences under substitution, it is important to keep in mind that they represent a *short-term* response to a very significant institutional change. Furthermore, there are a number of reasons for expecting the longer term or equilibrium response will be greater in character.

First, some of the concerns about the quality of low-cost substitutes that have operated to restrain substitution will lessen as the FDA actively seeks to clarify the technical uncertainties concerning drug equivalence. The FDA has taken the position that except for a relatively few drugs now under investigation for bioequivalence, any multiple source drug with an approved NDA or an abbreviated NDA is safe to substitute.[10] In addition, the proposed Drug Regulatory Reform Act discussed below would establish 'monographs' for all existing drugs and future NDA approvals which would establish explicit minimal standards of performance on all suppliers of a drug product.

Second, many of the large discount drugstore chains have strong economic incentives to substitute, and can be expected aggressively to promote the savings available to consumers from generics and lower cost products.[11] This is already happening in some urban areas. As consumers become more aware of these savings the demand for these lower cost products will increase.

Third, an increasing portion of the total prescription market will become subject to multiple sources of supply as the patents on a number of important drug products expire in the near future. Approximately one half of all prescriptions now involve multiple source drugs and this percentage has been increasing over time.

Finally, the form of substitution laws are changing in a direction designed to increase the degree of substitution. The most far reaching changes have occurred in states like Florida which amended their laws to require pharmacists to substitute lower cost drugs in stock for higher cost brand name medicines. Trade sources suggest substitution already is in excess of 10 per cent in Florida for leading multiple source products (Curran 1977).

9 For a recent survey of the experiences in eighteen states with substitution laws, see the *American Druggist*, October 1978, pp 12–17. An earlier more extensive analysis of the effects of substitution in Michigan was performed by Goldberg *et al* (1977). Interestingly, studies done to date suggest that for most (but not all) states, the prescriber has blocked substitution only in a very small percentage of cases. Pharmacists therefore have generally not exercised the option to substitute when legally authorised to do so.

10 This is spelled out very explicitly in a letter from FDA Commissioner Kennedy to New York's Commissioner of Health Whalen concerning that state's formulary for substitution. See *HEW News*, 23 January 1978.

11 Some analysis of this question has been performed by Curran (1977) in which the price cost-margins are compared for some representive brand name and generic drugs.

B Impacts on innovation

Substitution influences the expected revenues of a new drug entity only after its patent expires and rival producers enter the market (unless the drug is commonly licensed by the innovating firm). Hence, the impacts of substitution on the returns to R and D and pharmaceutical innovation will be directly related to the length of the patent life on a new pharmaceutical entity.

While the legal patent life is seventeen years, the effective patent life for NCEs in the pharmaceutical industry is typically much shorter. The reason is that firms generally apply for a patent early in the development cycle, well before a new drug candidate has cleared all the hurdles necessary for regulatory approval. Hence, by the time a drug is cleared for marketing, the remaining period of patent protection is much less than seventeen years. In doctoral dissertation research currently under way, Statman (1978) has estimated the effective life on new NCEs is now approximately ten years. Furthermore, David Schwartzman (1976) in an earlier analysis of this question found that the effective patent life was 12.4 years for all new NCEs introduced in the period 1970–73.

In order to gain some insights into how different degrees of substitution would influence the expected return to R and D, John Vernon and I have recently performed some illustrative calculations on this question. In order to undertake this analysis, we utilised the data on R and D costs and new product sales developed by David Schwartzman (1976) in his study on the expected returns from R and D. In particular, as the starting point for our analysis, we employed his projected revenue stream on a new NCE under the assumptions of a 20-year product life and a gross margin of 20 per cent. This case yielded an estimated 7.5 per cent after tax return to R and D. While the assumptions underlying this case are in fact Schwartzman's *upper bound* estimates on profit margin and product life, we feel they are more representative of what current NCEs can now expect to achieve, given the significantly fewer drugs now being introduced in comparison with historical circumstances. In any case, however, the purpose of our analysis is not to predict the effect of substitution on the return to R and D with exact precision, but rather to gauge the *sensitivity* of this return to alternative assumptions concerning the extent of substitution and the longevity of patent lives.

Some representative results from our analysis are presented in Table 2. These results underscore the fact that the effect of substitution on the returns from R and D is highly sensitive to the length of the patent life. In particular, we found that for an effective patent life of ten years, the rate of return to R and D was reduced from 7.5 to 6.8 per cent under a 20 per cent rate of substitution and to 5.6 per cent in the case of a 50 per cent substitution rate. On the other hand, if the effective patent life actually equalled the legal life of seventeen years, the effects of substitution would be much more modest in character. Even for the case of a 50 per cent substitution rate the rate of return would only be reduced to 7.1 per cent. These findings are obviously preliminary in character and could be expanded and refined in a number of ways. However they clearly illustrate the increased importance of patent rights to R and D incentives in a regime of increased government efforts to have low cost generic products dis-

TABLE 2 **Sensitivity analysis showing the effects of rates of return to R and D of different assumptions about the rate of substitution and the the length of effective patent life**

Percentage reduction in net income stream due to substitution	*Effective Patent Life*		
	10 years	*12 years*	*17 years*
−20	6·7	7·0	7·3
−40	6·0	6·4	7·2
−50	5·6	6·1	7·1

Notes:
(a) The standard against which the above rates should be compared is a 7.5 per cent return. This is Schwartzman's result for a 20-year commercial life and 20 per cent margin.
(b) It is assumed that at the end of patent life, repealing anti-substitution laws will result in the alternative reductions in revenues given above for the remaining years of the 20-year commercial life.

pensed by pharmacists.

In addition, substitution of generic products for brand name products already off patent and supplied by multiple sources (about one half of all prescriptions at present) would operate to shift cash flows from research intensive firms to non-research intensive ones, and hence reduce the supply of internal funds available to the former to undertake R and D investment. A number of studies have indicated that internal funds are a primary determinant of pharmaceutical firm R and D expenditures.[12] This finding is generally explained as reflecting a managerial unwillingness to borrow extensively to undertake R and D, given the high level of uncertainty that surrounds this investment. Whether firms would be willing to increase their current R and D to cash flow ratios if substitution were significantly to reduce firm revenues is also conjectural, given the low expected rate of return on R and D already observed in many studies.

Obviously, a full discussion of the merits of substitution laws, in all their different variants, is beyond the scope of the present paper. Nevertheless, however one feels about the desirability of promoting substitution, if these laws are successful in shifting significant revenues away from firms introducing innovations to generic competitors, they will clearly affect the expected return to R and D in a negative fashion. Our sensitivity analysis of these phenomena in Table 2, clearly underscores this fact. Furthermore, this analysis illustrates the importance of considering a policy measure suggested by several individuals. Namely, patent lives could be made effective with the date of NDA approval by the FDA, thereby restoring the effective patent life to the full legal limit of seventeen years. Our sensitivity analysis suggests that this would have a significant moderating effect on the negative impact of increased substitution on the expected return to R and D.

12 This result, for example, was found in my earlier study (Grabowski 1968) of the determinants of R and D in the pharmaceutical industry and in several studies in which pharmaceutical firms are included in a more general industrial sample such as the recent study by Robert Wilson (1977).

The Drug Regulatory Reform Act, considered below, was drafted as a comprehensive policy reform of government regulation of the pharmaceutical industry. The bill contains many provisions that go beyond issues strictly related to health and safety including many which are basically economic in character (eg, drug licensing, price posting, etc). However, the bill does not address the issue of declining patent lives, while including many provisions designed to facilitate generic price competition. This lack of attention to patent protection would appear to be a major deficiency in the proposed legislation.

IV The Drug Regulatory Reform Act

In introducing this reform legislation into Congress earlier this year, the Administration and its Congressional sponsors indicated that the proposed law would significantly expedite and encourage the availability of new drug innovations. The bill also formally declares this as a primary objective in its opening language. However, a close examination of the bill's many provisions reveals few specific measures that are likely to increase the incentives for innovation and several that would have the opposite effect. The focus of my attention in the analysis which follows are on these provisions that would especially influence drug innovation.

A Changes in the regulatory decision process

The bill would change regulation of the investigational (IND) process significantly. Introduction of the IND requirements in the 1962 Amendments has been cited by Dr Crout (1978) and others as one of the most important factors leading to higher costs and longer time-lags in clinical research and development. The new bill would create a two-stage process involving separate drug innovation and development phases. In the initial innovative phase (corresponding roughly to current Phase I and II of clinical research), the FDA would confine its regulatory overview to patient safety and would not attempt to evaluate research design or the scientific merits of research plans. It is argued that this would allow firms to obtain information more quickly on a drug's actions in man, which is important given the fact that the vast majority of drugs tested clinically do not become commercial products (less than 1 in 10). But it is not clear that this provision is *de facto* much different than current procedures. FDA's interest is now primarily on patient safety in early trials and firms do not generally prepare detailed research plans and protocols until they get some indication from clinical trials on a drug's safety and efficacy in humans.

At the same time, the bill would significantly expand FDA controls over the drug development stage. A new sixty-day hold period is established at the beginning of drug development investigations for FDA to evaluate research protocols. They are to be assessed on the scientific merits and validity of the research design as well as patient safety. Any proposed deviation in research design, arising from new findings, is also subject to formal approval and a further thirty-day hold period. Given what is known about the research and development process, with its frequent pattern of unexpected results and altered strategies, it seems unwise to institute such formal and potentially cumbersome regulatory controls over research procedures and methodology.

In addition to this tightening of controls over the investigative stage, the law also calls for increased holds and a longer period – 390 days compared to 180 days at present – to consider a new drug application. While the 180-day limit at present is a regulatory fiction, one would hope that a bill that imposed much tighter controls over the clinical investigative trials would be able to achieve faster processing of applications once they are received.

It is also important to recognize that as in the current law, there are no effective sanctions placed on the FDA for failure to meet prescribed deadlines. Given this and the fact that there would be several new decision points and holds added to the approval process, even the 390-day limit is probably very optimistic.

B Monograph versus NDA systems of drug licensing

A central feature of the new bill is the substitution of a monograph system of drug licensing for the current NDA approach. The current system essentially embodies the concept of an approved NDA as a private licence to a specific manufacturer and the related concept that the safety and efficacy data used to support the NDA have proprietary status as confidential commercial information.

The new law would establish public monographs for all new and existing drugs under which individual firms would then be licensed. The monograph would specify compendial type standards for a drug's indications and risk, purity, labelling and (where appropriate) batch certification. For drugs not currently on the market, these standards would be developed and approved prior to final FDA approval for marketing. As part of this public licensing concept, the original sponsor's data files on safety and efficiacy also would be made available to all interested parties prior to initial FDA approval for marketing. Subsequent applicants for licences to manufacture a drug under the monograph could make use of the original firm's data in support of their application, after a five-year period had elapsed.

The development of monograph standards is obviously designed to reduce the concerns about differences in product quality that have been raised with respect to cost containment policies discussed above – ie the MAC programme and state substitution laws. However, the development of such standards *prior* to the initial approval of a new drug is likely to place new and unnecessary burdens on the drug approval process. It will surely require more time and resources from regulatory authorities than the current system.

While the development of monograph standards prior to the entry of multiple sources of supply is desirable, it seems neither necessary nor desirable to burden the NDA approval process with this process. Most new drugs have patent protection that prevent competitors from legally marketing a new drug for several years after its introduction. Even if patent protection is weak or absent, the bill calls for a five-year period in which it is illegal to use the original drug sponsor's data to support a petition for licensure. Hence, in almost all cases the monograph could be issued at some appropriate time after NDA approval, but prior to the entry of generic suppliers. This would also allow it to incorporate the knowledge gained from larger scale post-market usage of new drugs.

C Early release of safety and efficacy data

The bill also would make publicly available all of the innovating firm's safety and efficacy data prior to the public hearing on monograph approval. This has been long advocated by the FDA for two basic reasons. First, it would allow outside scientists and other interested parties access to this information and thus allow them to participate in the approval decision process. Second, it would facilitate the entry of generic competitors after patents expire, since it would relieve these firms from doing any duplicate testing to establish safety and efficacy. At the same time, however, the release of all clinical data prior to approval could provide competitive firms with economically valuable information that would allow them to market generic and imitative drug products more quickly. This is especially the case in foreign markets where patent protection is limited or does not exist and where the availability of the clinical data might allow firms to gain faster registration with regulatory authorities.

A study performed by the Economic Analysis Group of the FDA (1978) has attempted to identify which foreign markets have a combination of both weak patent protection and stringent registration requirements so that early release of data could put the sales of innovative firms at risk. Their analysis indicated that over one-third of United States firm sales revenues are in such markets and include such countries as Canada, Spain, Sweden, Switzerland, and Brazil.[13] Of course the firms could counter these risks of lost sales revenues in foreign markets by delaying introduction into the United States until competitive positions in foreign markets are secured. But this behaviour would be completely counter to a primary objective of the new drug law – to expedite the approval of important new medicines into the United States.

The release of safety and efficacy data files also could aid rivals in both the United States and overseas in marketing imitative products that are so-called 'therapeutic equivalent' drugs – ie products which possess differentiated molecular structures but have similiar therapeutic effects. In particular, the availability of raw data files and research protocols could alert such follow-on firms to promising future directions for research as well as blind alleys to avoid. It also would provide insights into how to design the research protocols to achieve faster regulatory approval.

The optimal amount of protection to give an innovator in this area as well as in the length of patent rights gives rise to difficult trade offs which must necessarily balance desirable competing objectives. However, a number of eminent medical scientists have testified that a scientific summary (of scholarly research article length and substance) would adequately serve the objective of opening the regulatory decision process to interested members of the scientific community. Such a summary could be prepared by the sponsoring firm, subject to FDA approval, and released prior to an open hearing as proposed in the bill.

After the new drug is finally approved for marketing, the scientific

13 In particular, this analysis is contained in Fay Dworkin's paper of April 1978 (from the FDA's Economic Analysis Division) and also extended in the supplementary appendix (Tab C) of the 'The Analysis of Economic Impact of the Disclosure of Safety and Efficacy Data'. This is the FDA's economic analysis of this legislative proposal prepared under Executive Orders 11821 and 11929.

summary could also serve as the basis for licensing subsequent entrants without requiring any duplicate testing on safety and efficacy. As Dr Crout (1976) has indicated in prior analysis of this issue, there is rarely any duplicate testing done at present.[14] This is because sufficient information is generally available in scientific papers published by the innovating firm's scientists for the FDA to waive the requirement for additional testing on safety and efficacy. In addition, the FDA in its 1975 Freedom of Information administration regulations under existing law has declared it will make summaries of safety and efficacy data publicly available.

Although the scientific summary approach would not totally eliminate the disincentive effects on innovation considered above, there is reason to believe it would make a substantial difference. In this regard the FDA has made a preliminary investigation of the issue of foreign acceptance of data summaries. Their analyses indicate that a general summary of clinical trials (as opposed to a detailed summary of each trial) could substantially reduce the level of foreign sales at risk.[15] Hence, the use of scientific summaries rather than the full release of raw data files would appear to balance the various competing objectives here in a satisfactory manner.

D Provisional approval of new drugs

A number of analyses indicate that the 1962 Amendments requirement that effectiveness be demonstrated by 'substantial evidence, consisting of adequate and well controlled investigations', and the way this requirement has been implemented by the FDA, has been a major factor producing the 'drug lag' and related phenomena considered above. In particular, the FDA has chosen to delay approval until the 'pivotal' studies of efficacy have been performed even in the case of drugs which offer strong therapeutic advances over existing drugs and for which there is no reasonable scientific doubt about efficacy. The provisional approval section of the bill is addressed to this problem in that it would provide for provisional release of breakthrough drugs for use in life threatening or severely debilitating or disabling situations. It would substitue the criteria of 'significant evidence' for such drugs for the 'substantial evidence' concept that now applies. This is the main new positive incentive for drug innovation in the bill. Depending on how it is utilised by the FDA, it could be a positive step forward in speeding the availability of important new therapies.

At best, however, this provision will apply to only a very small fraction of new therapies. It should also be kept in mind that scientific advances in the drug areas, as in other fields, are often incremental in character, and frequently cumulate only gradually over time to major gains in social welfare. This has been the case historically for example, in anti-hypertensive therapy and combination chemotherapy for cancer.[16] Furthermore, the 'breakthrough' status of a new drug sometimes becomes apparent only after a drug is in general use and often for a different purpose than originally intended. The recently discovered properties of the drug Anturane in

14 Crout (1976), p 246.

15 See the FDA's 'Analysis of Economic Impact of the Disclosure of Safety and Efficacy Data', Tab C, p 4.

16 This issue has been discussed and analysed by Professor Wardell in a review paper prepared for the NSF's *Sub-committee on Regulation (1976)* and elsewhere.

reducing the probability of second heart attacks aptly illustrates this phenomena.

E Expanded post-marketing controls

The FDA's discretionary authority over post-marketing surveillance and distribution of drugs would be vastly expanded in the proposed law. First, the FDA is given broad authority to require post-marketing testing including testing on a non-intended use of a drug which the sponsor may have no commercial desire of pursuing. Furthermore, the FDA is also given the authority to restrict the distribution of a new drug to medical practitioners with specific training or in particular institutions. Third, the FDA would be able to remove drugs from the market place much more easily than under the current imminent hazard criteria.

A number of critics of current regulatory procedures have advocated greater reliance on post-marketing controls as a means of spurring innovation.[17] In particular, if such controls were used in a selective manner to expedite pre-market regulatory hurdles, this could improve the incentives for new drug innovation. However, if these post-market controls were employed as another regulatory layer on top of existing regulatory hurdles, it would obviously operate as a disincentive to innovation. It would seem important for Congress to send clear signals to the FDA on its intentions regarding these provisions in the language of the bill.

F The critical issue of regulatory incentives

Clearly a central fact that emerges from this very brief and partial review of the new bill is that it would significantly increase FDA discretionary authority at every point in the life cycle of a developing new drug product. It would institute tighter FDA regulatory controls over the drug investigational process, give FDA new powers to decide which drugs should be expedited through the various regulatory pathways, and also give significant new authority to the FDA over post-marketing testing and distribution of drugs.

At the same time, there are few, if any, institutional mechanisms in the bill for changing the incentive structure or attitudes at the FDA in order to ensure a more balanced decision-making environment for evaluating the benefits versus risks of new pharmaceutical products. Granting the FDA more discretionary authority under these circumstances could very well operate to slow down the drug approval process and further increase the costs of developing new drugs. It could thus have the exact opposite effects on pharmaceutical innovation claimed by its advocates.

Obviously, the incentive structure operation at the FDA is not an easy matter to change through legislative action. The new bill makes an admirable beginning in this regard by declaring that the encouragement of innovation is an important objective of public policy. However, beyond stating this objective, Congress should consider specific institutional mechanisms for ensuring that a more balanced perspective will in fact be reflected in regulatory decisions.

One idea that has been advanced along these lines which seems parti-

17 See the discussion of this issue in Grabowski (1976), ch 5.

cularly worthy of consideration is to create a distinguished panel of scientists and medical experts from elsewhere in the health community to review annually FDA's progress on new medicines as well as to consider potentially valuable new drug therapies already in use abroad.[18] This type of body would be a logical extension of the FDA advisory committees. However, in contrast to the latter, which become involved only in the later stages of the approval process for specific medicines, the proposed panel would have a broader oversight function and would be designed to bring the perspective of scientists and medical prescribers of drugs into the regulatory decision process in a more complete and systematic way.

In addition, the FDA might be required to include specific evaluations of its regulatory policies on innovation in its annual report and also to issue 'research impact' statements when instituting new administrative regulations.

While the effectiveness of all these policies is open to question, it would seem worth experimenting with such measures in order to try to generate a more balanced decision-making environment, especially if FDA discretionary authority is to be significantly increased in the various ways proposed in this new legislation.

V Summary and conclusions

The above analysis indicates that the prospects for pharmaceutical innovation are not particularly optimistic at the present time. On the one hand, FDA regulatory policies have dramatically increased the costs and development time to innovating firms, while reducing the average length of time that a new pharmaceutical product typically enjoys in terms of patent protection. On the other hand, product substitution and cost containment policies are likely to intensify the pressures on the sales revenues of new products once their (shortened) patent life expires. This type of environment is therefore likely to exacerbate the adverse trends for drug innovation already in progress unless some specific policy measures are devised and implemented to offset these policy developments.

Administration officials have pointed to the proposed Drug Regulatory Reform Act of 1978 as containing a number of positive new incentives for pharmaceutical innovation. This would seem, however, to be a very debatable proposition. The bill would vastly increase the discretionary authority of the FDA over the development, introduction, and post-marketing surveillance of new drugs. At the same time, there is little reason to believe that the provisions of the bill would alter the incentive structure or attitudes at the FDA to ensure a more balanced decision-making environment for evaluating the benefits versus risks of new pharmaceutical products. Granting the FDA more discretionary authority under these circumstances therefore could operate to slow down the drug approval process rather than expediting the availability of new drug therapies.

While my analysis of the immediate prospects for innovation has been somewhat pessimistic in character, there are some positive developments in the current situation. The Drug Regulatory Reform Act does introduce

18 For further discussion of this concept, see Grabowski (1976), ch 5.

for the first time the objective of encouraging innovation as part of the public policy mandate in regulation. Furthermore, the bill is being legislated against a background of growing general policy concern about lagging United States innovation and productivity growth. Many administration and Congressional members see the need for changes in federal policy, including regulatory policy, to address this problem.[19] These emerging changes in public perceptions and priorities may yet produce legislation that is substantially more committed to encouraging innovation than is presently the case.

19 In this regard, the administration has recently appointed an Inter-agency Task Force under its Scientific Advisor to consider the issue of lagging innovation and to make appropriate policy suggestions.

REFERENCES

Caglarcan, Erol, Richard Faust and Jerome Schnee. 'Resource Allocation in Pharmaceutical Research and Development', in S A Mitchell and E A Link (eds), *Impact of Public Policy on Drug Innovation and Pricing*. (Washington, DC: American University, 1976).

Cocks, Douglas L. 'Product Innovation and the Dynamic Elements of Competition in the Ethical Pharmaceutical Industry', in Robert B Helms (ed), *Drug Development and Marketing*. (Washington, DC: American Enterprise Institute, 1975).

Crout, J Richard. 'New Drug Regulation and Its Impact on Innovation', in S A Mitchell and E A Link (eds), *Impact of Public Policy on Drug Innovation and Pricing*. (Washington, DC: American University, 1976).

Curran, John P. 'Multi-Source Drugs: An Acceleration in the use of Lower Costing Substitutes'. Reynolds Securities Information Report, May 1977, New York.

Federal Food and Drug Administration. 'The Analysis of Economic Impact of the Disclosure of Safety and Efficacy Data'. Mimeo. Washington, 1978.

Goldberg, Theodore, G W Aldridge, Carolee A DeVito, Jerry Vidio, Willis E Moore and W Michael Dickson. 'Impact of Drug Substitution Legislation: A Report of the First Year's Experience'. *Journal of the American Pharmaceutical Association*, April 1977.

Goldberg, Theodore, Carolee A De Vito, David Smith, Miron Stano, Jerry S Vidio, Willis E Moore and W Michael Dickson. 'Evaluation of Economic Effects of Drug Product Selection Legislation'. Paper presented to the American Public Health Association Meetings, Washington, DC, October 1977.

Grabowski, Henry G. 'The Determinants of Industrial Research and Development: A Study of the Chemical, Drug and Petroleum Industries', *Journal of Political Economy*, March/April 1968.

Grabowski, Henry G. *Drug Regulation and Innovation: Empirical Evidence and Policy Options*. (Washington, DC: American Enterprise Institute for Public Policy Research, 1976).

Grabowski, Henry G and John M Vernon. 'Consumer Protection Regulation in Ethical Drugs', *American Economic Review*, May 1977.

Grabowski, Henry G, John M Vernon and Lacy G Thomas. 'Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry', *Journal of Law and Economics*, April 1978.

Grabowski, Henry G. 'Regulation and the International Diffusion of Pharmaceuticals'. Paper presented to the American Enterprise Institute Conference on the International Supply of Medicines, 15 September 1978.

Hansen, Ronald W. 'The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes'. Mimeo, University of Rochester, October 1977.

Kennedy, Donald. 'A Calm Look at 'Drug Lag', *Journal of the American Medical Association*, 30 January 1978.

Reekie, W Duncan. 'Price and Quality Competition in the United States Drug Industry, *Journal of Industrial Economics*, March 1978.

Schwartzman, David. *Innovation in the Pharmaceutical Industry*. (Baltimore: Johns Hopkins Press, 1976).

Statman, Meir. 'Incentives, Regulation and Drug Innovation', in process, Columbia University, 1978.

Virts, John. 'Research and Development, Expectations and Returns on the United States Pharmaceutical Industry', in process, July 1978.

Wardell, William and Louis Lasagna. *Regulation and Drug Development*, (Washington, DC: American Enterprise Institute for Public Policy Research, 1975).

Wardell, William. 'Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Britain from 1972 to 1976', Mimeo, University of Rochester, November 1977.

Wardell, William. 'A Close Inspection of the 'Calm Look' ', *Journal of the American Medical Association*, 12 May 1978.

Wilson, Robert W. 'The Effect of Technological Environment and Product Rivalry on R and D Effort and Licensing of Inventions', *Review of Economics and Statistics*, May 1977.

Present problems: The effects of British regulations

Brian Cromie, FRCP
Director, Hoechst UK Ltd.

Introduction

It is perhaps appropriate that I should be speaking at this time and on this subject.

The time is right because the year 2000 is just about twenty-one years away and I joined the pharmaceutical industry just twenty-one years ago. I can, therefore, sit at this mid-point looking back on the effect of drug regulations so far and then look forward from that base to the future.

It is also right to consider today what effect regulatory requirements will have in the future, because that is when today's regulations will have their impact. It now takes around 10–12 years to develop a new medicine for the market and much longer if new animal models have to be set up; so additional regulatory requirements made this year or next year will be having their effect on medicines that would have been available in the early 1990s.

This time-lag is a great psychological problem, as people often ask why the pharmaceutical industry complains about excessive regulatory demands, when they see that new medicines are still coming onto the market. Such people forget that today's new medicines were started in 1967 or so, when regulatory requirements were relatively basic, and we have yet to reap the barren harvest brought about by the regulatory requirements added since those days.

Regulatory authorities

Regulatory authorities must have the sympathy of all reasonable men, as they have an impossible and thankless task.

a) Opposing forces

Directly or indirectly, they come under pressure from politicians, vocal minority groups whose voices are exaggerated by the media and to some extent from the pharmaceutical industry, whose products they keep from general availability. They are unlikely to receive much public plaudit for speeding new medicines through the regulatory processes but they will certainly be blamed if a forseeable or even an unforseeable hazard was missed in an attempt to prevent the current delays.

b) Potential for Harm

Regulatory authorities have tremendous potential for harm in preventing improved therapy from reaching patients that need it. It has been suggested that the 11 years of delay in introducing beta-blockers into the US for indications other than arrhythmias, killed a quarter of a million Americans.[1] These 'mass-murder' activities of regulatory authorities are

not just limited to delays in processing applications and issuing product licences, they are there because of the very existence of regulatory bodies and their requirements. The delay of six months to two years in handling licence applications is nothing compared to the prolongation of drug development time and the restrictions of innovatory research brought about by the presence of regulatory authorities and the data, which they formally demand or informally suggest might be required.

You may feel that I have fallen prey to slight exaggeration if I describe drug regulatory authorities (DRAs) as 'mass murderers', when they were established to protect patients but their potential for harm must never be overlooked.

c) Balance Required

Leading European clinical pharmacologists meeting in September 1976 to discuss the problems of DRAs recognised that they were set up to protect patients but have been pushed into defensive attitudes, so that 'some regulatory agencies are now requiring such concentration on safety that the benefits to patients are actually being jeopardized'.[2]

They go on to show the escalating demands of doubtful validity and say that 'A balance must be found between the benefits of prolonged studies of safety and the possible deprivation of patients.'

Regrettably that balance has not been found and continues to tip in the direction of increasing requirements, irrespective of patient deprivation.

I admit that the recent statement in the US of the Drug Regulatory Reform Act is beginning to make the right sort of noises and extracts of some of their ideas are shown below:

a) To get valuable drugs on the market as quickly as possible . . .
b) To make drug regulation more rational and understandable . . . risks have to be weighed in the light of benefits.
c) To stimulate drug innovation and research.
d) . . . ending arbitrary regulatory distinctions . . .

(Drug Regulation Reform Act 1978, *US–HEW)*

However, these encouraging sentiments were partially counterbalanced by the phrases such as 'not compromising safety requirements', 'publicising experimental data' and 'expand the FDA's enforcement powers'. It would be great to see the FDA lead the world in a more positive approach to practical drug clearance but doubts have already been expressed and we will have to wait and see.

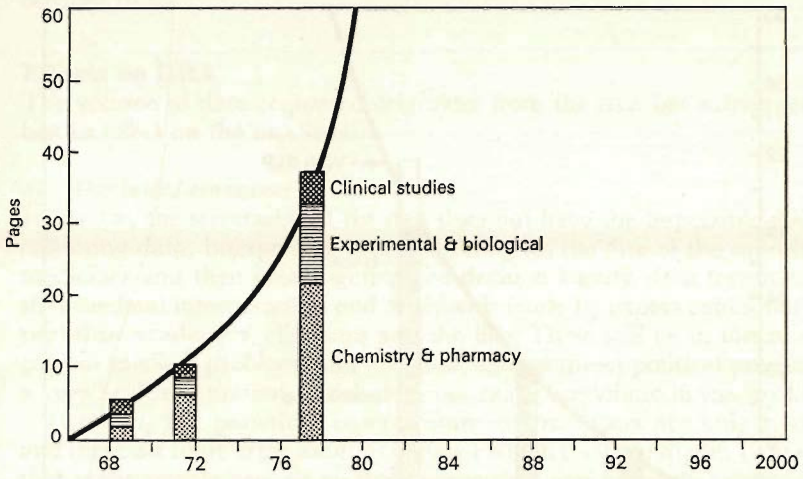
DRA requirements

DRA requirements were initiated in the light of knowledge at the time of their introduction and often designed to try and guard against some particular danger.

a) Old tests retained

In the years that have passed, knowledge must have changed and there

FIGURE 1 **C.S.M./D. Guidelines**



should be increasing recognition of the validity, or lack of it, of many tests.

One might, therefore, expect that older tests would be abandoned and new procedures introduced which are more relevant. Unfortunately, I do not know of a single significant reduction; all that has happened is that more and more tests have been added.

Perhaps, we in the UK should be careful in complaining too vociferously when we look at transatlantic comparisons. One reported drug submission consisted of 72,200 pages in the US and only 857 in the UK.[3]

b) Measuring DRA requirements

Pages of paper do not, of course, necessarily reflect the work that has been done to fulfil DRA requirements but it is certain that these have increased in the UK.

One simple measure is the length of the CSD or CSM guidelines. As shown on Figure 1 the guidelines increased from four pages in 1968 to ten in 1971 and then to over thirty-seven pages in 1977.

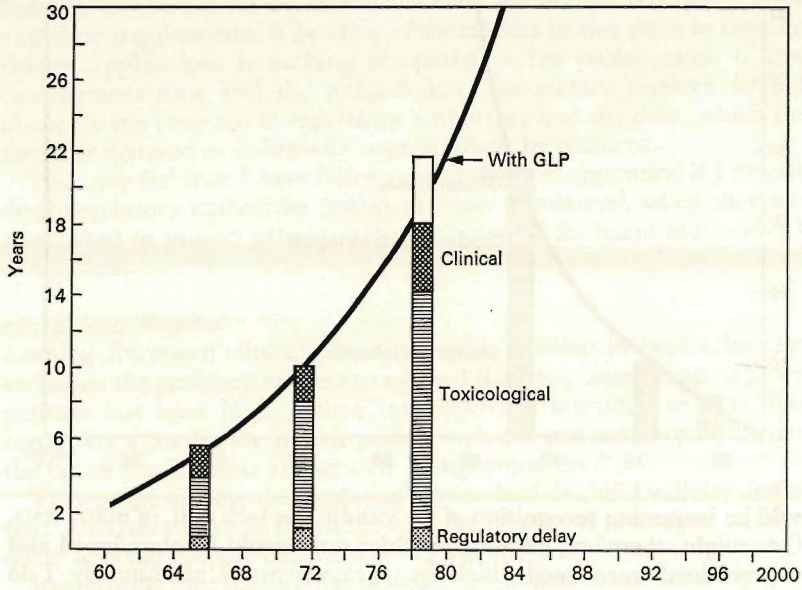
Figure 2 shows the average duration of the tests requested by the CSM for a chronically administered medicine. Many of these tests would be conducted in parallel but an addition of the total duration gives a good idea of the work involved.

It has been estimated at 5.4 years for 1965, 10.0 years for 1971 and 17.6 years for 1978. Perhaps this last should really be 21 years with the addition of Good Laboratory Practice[4] to our UK registration work, which also has to be submitted as part of an NDA to get world-wide registration.

c) Extrapolation to future

The frightening aspect of this is the growth of the toxicological element, referred to by the Workshop of European Clinical Pharmacologists as tests which have 'developed arbitrarily and by casual accretion'[2] and the slope of the curve. At this rate, the medicines available in the year 2000 would need about 100 years of work before Product Licence submission.

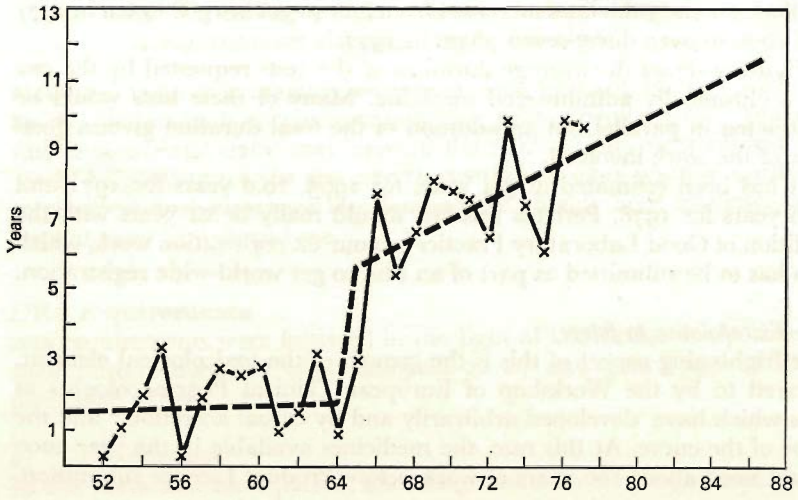
FIGURE 2 **Work/Years for P.L. of chronic N.C.E.**



d) Marketing Delays

It follows from the registration requirements that the time between patenting and marketing will increase. Figure 3 gives an analysis of the time between first publication and marketing for over 200 medicines. The projection of the current trend shows that the recently extended patent life of a new medicine will have expired prior to marketing by about 1990 and it is unlikely that anybody will invest in basic research in the knowledge that it will only produce unpatented products.

FIGURE 3 **Time lag between 1st publication and marketing**



Unless somebody calls a halt, the inevitable results of these trends is obvious to all.

Effects on DRA

The volume of data requested originates from the DRA but subsequently has an effect on the DRA itself.

a) Overloaded committees

In the UK, the secretariat of the DRA does not have the impossible task of collecting data, interpreting them, deciding on the fate of the submitted medicines and then promulgating the decision legally. It is fortunate in that the final interpretation and decision is made by expert committees of part-time academics, clinicians and the like. These will be in touch with current medical problems and are proof against direct political pressure – a very healthy situation, which does not exist everywhere in the world.

However, the part-time expert committee members are only human and there is a limit to the amount of paper which they can digest. I am sure that many people here sit on such committees and know that depressing moment when you sit down at home on the week-end before a meeting and try to wade through piles and piles of paper. It can be a soul-destroying experience, particularly if the secretariat have not given you sufficient time to really do the job properly.

b) DRA summaries

In the face of this mountain of data, the part-time experts are forced to rely more and more on the summaries put forward by the secretariat. It would be a retrograde step if this meant that the independent experts were increasingly influenced by the opinions of the secretariat but, fortunately, in the UK, this is balanced by the practice of asking manufacturers to submit their own summaries. These are cleared by the secretariat and can be the basis of the documentation read by expert committees, just referring to the total data to check important points.

c) EEC

In contrast to this simplification in the UK, the prospect in the EEC looks grim. Directives put forward by groups of DRA officials will tend to centralise power and any form of European registration on the CPMP model will, inevitably, decrease the input of manufacturers by reducing dialogue and increase the decision-making influence of full-time bureaucrats.

Regretfully, any centralization on a multi-national basis is likely to combine together the DRA requirements of the various countries and then add some more of their own. However intelligently worded the first draft directives may be, we will end up with demands for more and more work and the curve I showed earlier will continue to move towards infinity.

Surely some day somebody will see this and say stop!

Effects on pharmaceutical industry

The effects of increasing DRA requirements on the pharmaceutical industry

are many and varied and the trends seen today will escalate. They involve documentation, innovation and diversification.

a) Documentation

In the face of DRA requests, whether formal or just an informal hint by a single assessor, the industry tends to comply. Even though their own experts and their common-sense tells them that certain tests are an invalid waste of time, it often seems easier to do the extra year's study in goldfish than to argue the case and risk a delayed submission or an adverse summary from that assessor to the relevant committee.

In this respect the industry is its own worst enemy and is contributing to its own destruction.

I suspect that they will continue to do this to an even greater extent if we move towards EEC registrations because of the greater involvement of full-time bureaucrats and because more markets will be involved.

The reverse trend is seen when dealing with the committees of part-time experts.

The industry is already realizing that the committee members just cannot take in all the evidence submitted and are dependant on recommendations by the secretariat. They are, therefore, engaging with increasing frequency in 'appeals' or more accurately 'hearings'.

There are now many examples where the company involved has presented virtually the same evidence at a hearing as was included in the submission but the original rejection was reversed, just because the committee was able to hear and understand the data in a realistic context.

Such presentations of data are extremely time-consuming for the committee and for the industry but it is inevitable that they will increase, if the volume of the DRA requests continue to increase.

b) Innovation

Advances in therapy are generally assumed to be more difficult today than in earlier years but no advances will be made unless true innovatory research takes place.

Innovation throughout the whole pharmaceutical industry is decreasing, as increasing proportions of R and D budgets are devoted to regulatory requirements.

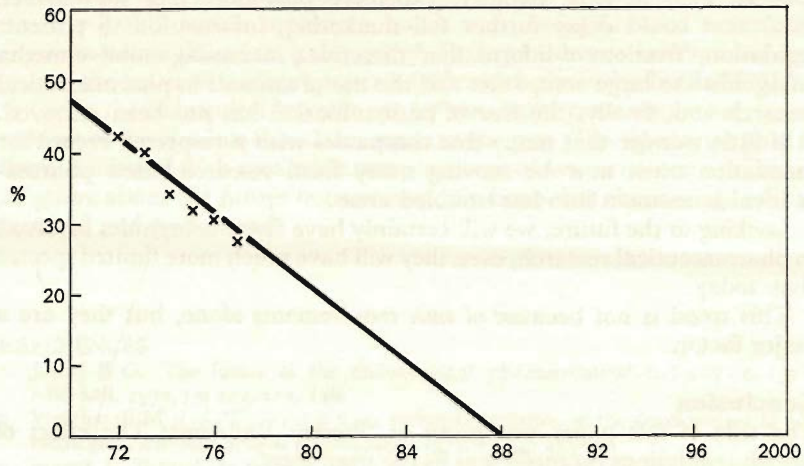
The Workshop of European Clinical Pharmacologists[2] stated, of today's regulatory requirements, 'there is much evidence that they impede innovations'.

Evidence can only be gained from the companies involved and, as an illustration, I can quote from my own company Hoechst, one of the largest research-based pharmaceutical companies.

Hoechst now has a pharmaceutical annual research budget of approximately £100 million, which can now only increase as costs increase, so that the true level of expenditure remains more or less constant. However, as shown on Figure 4 the percentage devoted to innovatory work has decreased from 42 per cent in 1972 to 28 per cent in 1977; a fall of one-third in five years.

There is always a danger in extrapolation of such figures but, if this were

FIGURE 4 **Percentage of Hoechst world-wide R+D budget devoted to innovation.**



to come about, the innovatory activity of the largest pharmaceutical company in the world could cease completely in 1990.

There are similar reports from other major research-based pharmaceutical companies. Some quote different percentages, due to different definitions of 'innovatory' research work, but the downward trend is the same.

c) Diversifications

Pharmaceutical companies are commercial organizations and must consider returns on shareholder's investment but exactly the same problems would arise, if the industry was state-owned and had to consider returns on taxpayers' money.

The research director of Hoechst recently stated[5] that the research-based pharmaceutical industry does have a future, as it has proved to be the best method of providing therapeutic advances and that this will eventually be recognized by society.

I hope he is right.

In the meantime, there is little to encourage anybody to invest in pharmaceutical research with the return on investment in the UK being about 6 per cent in 1974 and nearer 3 per cent in 1975 and 1976, while the average for industry remained around 10 per cent.[1] It is, therefore, no surprise that mergers and diversifications into other areas continue, and that companies withdraw from basic research[6] or move towards product development or licensing: neither of which gives new chemical entities for therapeutic advancement.

As an example, a leading pharmaceutical company with an R and D budget of £17 million released its list of new products over the last two years;[7] four were licensed compounds and only one minor product, which was a purification of a naturally occurring substance, came from their own laboratories.

It must be admitted that this withdrawal from pharmaceutical research

is not just due to DRA requirements. There are also problems of limited return with price control, WHO lists and UNIDO 'packages'. There is also concern over no-fault liability, expensive post-marketing surveillance (PMS) that could delay further full marketing, information to patients legislation, 'freedom of information' directives, increasing emotive media antagonism to large companies and the use of animals in pharmaceutical research and, finally, the fear of nationalisation has not been removed. It is little wonder that many fine companies with a respected record for innovation must now be moving away from research-based pharmaceutical investment into less troubled areas.

Looking to the future, we will certainly have fewer companies involved in pharmaceutical research, even they will have much more limited spectra than today.

This trend is not because of DRA requirements alone, but they are a major factor.

Conclusion

The title of this paper was given as 'Present Problems; The effect of British regulations on medicines in the year 2000'.

The continuation of the trends of our 'present problems' shows that regulatory requirements will be infinite and pharmaceutical innovatory research zero well before the year 2000.

The trends are there for all to see but the questions must be asked; will it really happen? and does it matter?

Taking the second question first, the answer must be yes. Even for established therapies, the room for improvement is considerable because of resistance to current treatment or its non-optimal therapeutic ratio. In addition, as stated by the Workshop of European Clinical Pharmacologists[2], 'There remains a large number of diseases for which new drugs are needed as urgently as ever, and advances will be achieved only if research and development are actively encouraged.'

Coming back to the first question; regulatory requirements will become infinite and pharmaceutical innovation will be virtually extinct unless the warning signs are heeded and action is taken.

That leads to the third question; what could and should be done to prevent this outcome?

Many of the answers are fairly obvious and have been suggested before.[2,6] They must include:

a) Revision of all DRA requirements and rejection of any test of unproven validity.
b) Earlier use in man.
c) Earlier marketing with substitution of animal toxicology in invalid species by a workable system of PMS.
d) Ensure that multinational registration systems, such as the EEC, accept the principles of (a) to (c) above and do not ask for any work to be repeated, except perhaps some local confirmatory clinical work.
e) Reconsider purely bureaucratic devices, such as 'Good Laboratory Practice' and 'Good Clinical Practice' before they engulf the world.
f) Look again at medicines as 'special cases' for longer patents and exclusion from no-fault liability.

g) Educate public, politicians, pressure groups and regulatory bodies themselves to understand that no medicine is entirely safe and that striving after complete safety will just abolish all effective medicines. The public wants medicines but it must recognize and accept the risks which these inevitably carry. Perhaps this was best summarised on the cover of a recent paper-back[8] which showed a bottle of tablets with the inscription 'TO GET RELIEF YOU MUST TAKE SOME RISK'.

Most of these points have been made in the past. The lip-service paid to them combined with an almost complete lack of action does not make me sanguine about the future but one can only hope that the message will be received and understood.

REFERENCES

1 James B G. 'The future of the multinational pharmaceutical industry to 1990'. ABP Ltd, 1977, pp 102, 103, 148.
2 Weatharall M *et al.* 'Towards a more rational regulation of the development of new medicines'. *European Journal Pharmacology*, 1977, *11*, pp 233–38.
3 Burger A. 'Behind the decline in new drugs', C & EN. 1975 (September), 22.
4 Paget E. 'Quality Control in Toxicology'. MTP Press, 1977.
5 Gareis, H G. 'Press Conference on Pharmaceutical Research'. Frankfurt Hoechst, 10 – 11 November 1977.
6 Cavalla, J F. 'Innovation in the Pharmaceutical Industry'. *British Medical Journal*, 1978, *1*, 1486.
7 Lasagna L. 'International Drug Regulation'. Reprint No 73, September 1977. Centre for Health Policy Research.
8 Laurence D R and Black J W. The Medicines You Take'. 1978, Fontana Books, London.

Discussants

Mr A. J. MERIFIELD *(Department of Health and Social Security, Britain)*

It seemed that the speakers this afternoon were saying that unless public policies allow companies to make a profit, they will not invest in research and development. With that background, I think it is interesting to note from the Office of Health Economics' own publication that from investing just over £80 million in research and development in 1975, companies in Great Britain virtually doubled their investment to approximately £150 million in 1977, so perhaps they are on the side of the angels. Equally, I think it is significant that our own returns show that about 12 per cent of the value of sales is invested in research and development in Great Britian, which compares to a figure of something like 7.5 per cent mentioned by David Schwartzman in some of his books.

It seems that one of the burdens of this afternoon's talk has been that government is 'an intruder'. May I mention two aspects of government interest which seem to be now part of our scene.

Firstly, the Government is increasingly the payer of the bills. To take pricing as an example: the Department of Health and Social Security (DHSS) in the United Kingdom is a major buyer and market forces do not work in the regular way. The person who needs the drugs does not order them; the person who orders the drugs does not pay for them. Therefore, as a major buyer, like any other major buyer (whether a company or another government department), we seek reasonable terms for the drugs that we purchase. However, we are not simply concerned – in words, I think, that were used in one of the papers – in crude terms 'to minimise costs'. We have an interest, and it is stated in our agreement with the industry, to see that the Pharmaceutical Price Regulation Scheme enables the industry to be strong, efficient, profitable and research-based; and also that our administration of the scheme should take into account the circumstances of individual companies, whether those circumstances relate to investment, export or research. As most of those present know, the price regulation scheme allows research costs as 'costs', which is an important factor when we consider the position of individual companies within the United Kingdom industry as a whole.

I do not think that the way in which we go about our price regulation functions props up companies which are not successful. Nor indeed does our scheme seem to stop research and development. Nor would the scheme prevent the downward path of research-based companies which were unable to sustain their success by more innovation. In that respect, may I pick up one point from this morning. I think that concern was expressed about the problems of producing drugs for tropical countries, and drugs for the over sixty-fives. Certainly the production of drugs for tropical countries imposes a considerable number of problems. When one looks at the drugs for those aged over sixty-five in the United Kingdom, one might say that the price regulation scheme that we run does allow the cost of that research to be taken into account as costs, and once the drugs are produced the Department of Health would purchase them, because

that is what 'the public' will demand.

Also, I think that our scheme is not too rigid. There is no real black and white in this situation, and although some recent reports might have suggested otherwise we have no intention of departing from the flexible approach which has been used so far. We seek to attain a balance between the legitimate needs as we see them of a major purchaser and the needs of the industry. If I may digress for a moment, I think Professor Schwartzman mentioned that Cooper's study showed that the cost of drugs in France was lower than that in Britain. I think that one line of Cooper's study also showed that the top twenty United Kingdom drugs were cheaper than those in France. If the industry feels that that is an indication of price regulation pressures, perhaps I should say that that represents in today's terms a profitability for the industry running around 18 per cent, which even after tax gives a return of 9 per cent or thereabouts. This is somewhat higher than the figures of 3 per cent, 6 per cent and 7 per cent mentioned in other papers.

To turn briefly to governments' second interest, in drug safety and registration. I think that in an age of greater consumer awareness, and the litigation that brings, the greater scientific knowledge which enables people to identify side effects, and the longer periods over which drugs are now used (so that people who might have been treated for only three or four years are now living longer and the drugs are entering a sort of second phase of life), will inevitably give rise to public concern. It seems that the question to ask this afternoon is: would companies themselves not be taking that into account in some of their own measures regarding the testing of drugs?

Although this is not particularly in my direct field it would seem that regulatory committees, particularly where they include outside experts, should be able to take into account legitimate public concern, and at the same time fit the requirements of the tests to what is practical in the circumstances and balance a controlled risk against the need for caution. It seems to me important that some of the discussion should continue in that area.

Certainly we do not want unnecessary duplication in registration, and a number of those present are involved in harmonisation. By that, I hope we do not mean just a piling up of one set of regulations on top of another, but flexibility. Guidelines are guidelines, they are not directives. And there is a need for approachability – the spectre of a large central registration bureaucracy is as chilling to us in government as it probably is to most of those present.

Dr M. NOVITCH *(Food and Drug Administration, Department of Health, Education, and Welfare, United States)*

I would like to make a few brief comments on the very comprehensive presentations that we have heard today and then say a word about two initiatives that were discussed in some detail by Professor Grabowski that are helping to shape United States public policy in the pharmaceutical sector. They are the proposed Drug Regulation Reform Act and the financing of drug benefits in the public sector.

Professor Grabowski expressed concern about declining rates of drug innovation – the drug lag – in the United States. My colleague, Bill Wardell, has criticised the Food and Drug Administration (FDA) for steadfastly denying the existence of a drug lag and at the same time promising to eliminate it. I confess to having considerable difficulty in interpreting the data on drug innovation. The current data appear to show that while the total number of drug introductions has declined in recent decades, most of that decline has occurred in duplicate products and in combinations of drugs, while the approval rate of newly synthesised drugs has been comparatively steady. In fact, in the last decade, the trend in approvals of new drug entities has been upward. In the late 1960s, nine or ten new drugs could be expected to be introduced in the United States each year. In the past two years, the number has increased to between 15 and 18. Dr Wardell finds that the lag between the United States and Europe (as he defines and measures it) is narrowing, and if Dr Cromie's projection proves to be accurate, namely that by the year 2000 it will take one hundred years to get a drug approved in Europe, we may soon find the lag to be moving in the opposite direction!

I should like to add a few comments to Professor Grabowski's excellent summary of the Drug Regulation Reform Act. We have now completed in the United States six months of hearings by the health committees of both houses of the Congress. I must say that the quality of debate has been remarkably good and rather free of the acrimony we sometimes see when changes in drug laws are proposed. With few exceptions, the drug community in the United States seems convinced of the need, if not agreed on the direction, for change. In both the House of Representatives and the Senate, the bill has been undergoing revision and the respective committees are nearly ready to report on revised bills. It is fairly evident from the hearings that the idea of decreasing government regulation of initial research efforts is favourably regarded. That is a major element of the Administration's proposal, but the House committee may be prepared to go even further, placing more oversight responsibility for drug innovation on local research institutions. There is general agreement on the need for special provisions to expedite the approval of truly life-saving, so-called 'breakthrough' drugs. I think that provision will be retained in the final legislation. There is also agreement on the need to revise criteria for admission to the market to include an explicit weighing of benefits and risks. The terms in the present Act, 'safe and effective', seem to imply to many in the public a sense of absolute certainty that an approved drug must be safe and always effective. We know that often neither is the case. Therefore an explicit mandate for the FDA to weigh benefits against risks would be desirable. It certainly would help increase public understanding of the drug approval process.

The proposed legislation would assure a more public approach to drug approval, and the making of at least some scientific data on drugs available to the public. The question is how much and when. The administration proposal would release all of the data to the public at the time of application. I sense that if there is any major change imposed by Congress, it will be in the direction of making summary data public, at least initially, with more or all of the data being laid before the public some years after a new

drug is approved.

There is also fairly good agreement on the need to separate the process of approving a drug entity from approving a licence to market it, although there is some discussion of combining those actions at the outset and separating them later in the interest of expediting drug approvals.

Obviously, there are many other important provisions of the proposed law that time does not permit me to discuss.

I cannot predict whether Congress will complete its work on the legislation this year. If the bill should fail to gain passage at this session, it will surely be re-introduced next year, and I am confident that major reform of the drug approval system will become law.

In the area of health care financing, the administration has completed a statement of principles that will guide the Department of Health, Education and Welfare (HEW) in developing a more detailed national health plan. It is too early to predict to what extent drugs would be covered initially, if at all, under national health insurance but there is no question that health insurance of any kind will induce some additional demand for drugs. Public financing now accounts for about one-third of the more than $10 billion spent on drugs in the United States. In this area, current State and Federal policy is to avoid direct controls on drug prices, and instead to try to encourage price competition by eliminating the remaining existing State anti-substitution laws, by promoting generic competition among multiple-source drugs, by informing prescribers about price differences in both single and multiple-source drugs and by limiting payment under the public programmes to competitive prices through the maximum allowable cost (MAC) programme.

In sum, policy in the United States, as I think has been well stated by earlier speakers, is aimed at taking advantage of open and competitive market forces, first by reducing barriers to drug research and development and expediting the approval of the drugs consistent with a mandate to protect public health and second by increasing price competition, particularly among multiple-source drugs.

PROFESSOR W. M. WARDELL *(University of Rochester, United States)*

We have heard this afternoon about the many factors that influence drug research and development and innovation, Of these, most attention, until fairly recently, has been given to what one might call the 'directly acting' influences on research – for example, those laws and regulations that control clinical research. The IND provision in the United States and the Medicines Act here determine what standards of evidence are necessary to show that a drug is adequately safe or effective. These are direct also in the sense that they control how the research is to be done. Their influence on *whether* the research will be done is, however, less direct.

What is becoming increasingly apparent – and I learnt a great deal this afternoon also – is the large effect that what one might call the *indirect* factors are having, and potentially have, on research: factors that do not simply control how research is done, but that determine whether it will be done at all. They are, in particular, drug utilisation controls, as I discussed

in my recent book.* What I did not fully realise at the time was the huge significance, within the general framework of utilisation controls, of the regulation of drug prices and of things like substitution laws, in controlling both research and the practice of medicine. When I first began to get interested in the factors controlling utilisation, I was thinking of it mainly from the point of view of those things directly affecting the physician – for example, the impact of third party formulary controls that almost all national health services except the United Kingdom have. (For example, Australia, New Zealand and Norway are classical examples where the regulator of the health care system can control how drugs are to be used.) Although I mentioned it in the book, I did not really appreciate the profound influence that substitution and other pharmaceutical reimbursement practices are having, and are going to have, on research. That was well described by Professor Schwartzman and Professor Grabowski.

I think we must realise that the fundamental importance of these economic factors needs to be appreciated, especially by the medical profession and by patients. Most of us who have looked at substitution as a problem have really thought of it as affecting patients only if there are scientific issues involved, such as bio-availability problems. One does not normally take the step of investigating whether research will be performed as a result of those. I hope as a result of today's presentations, there will be much better understanding of that aspect.

The general significance of utilisation controls, of which drug reimbursing practices are a part, is that they are impinging, or are beginning to impinge, on all countries of the world that are both the major performers of research and the major markets, so that both the decisions to do research and the way in which it is done are under pretty tight control. That is quite unprecedented, historically; we shall not know its full effects on innovation for fifteen to twenty years, because of the various factors alluded to. We do not even have any effective techniques for measuring whether innovation is falling off, and even if we could detect a decline in innovation we do not have any policies ready with which to respond. For the year 2000, we need at least the following: firstly, something rather simple, a full public appreciation of the central importance of innovation. The American Association of Retired Persons, for example, believes that what we need is to obtain yesterday's drugs more cheaply. I believe that they, and everyone else, would be better off if we could obtain tomorrow's drugs sooner. Secondly, we need a mechanism to recognise when pharmaceutical innovation (and, by extension, many other technologies and systems) is being inhibited and what is the medical and social impact of such inhibition. Finally, we need a policy mechanism for responding to the threat or the perceived threat of imminent diminution of innovation, with some realistic appreciation of the most effective role of the public and private sectors as both creators and consumers of innovation.

*'Controlling the use of therapeutic drugs: an international comparison'. William M. Wardell, Editor. American Enterprise Institute for Public Policy Research, Washington DC, 1978.

GENERAL DISCUSSION – SESSION II

Two central themes emerged during the discussion which followed the papers and prepared comments presented to the second session of the symposium. The first concerned the dual and seemingly conflicting functions of the Department of Health and Social Security (DHSS) in its dealings with the pharmaceutical industry. On the one hand its role could be seen as that of a regulatory authority with direct controls over the development, marketing and promotion of drugs and powers, although lacking legislative stature, to influence pharmaceutical prices. On the other hand the DHSS is the sponsoring Department for the industry and is therefore keen to assist the latter's performance, especially in the field of exports.

Mr G. J. Wilkins, the chairman of the session, first drew attention to this dual role. He contended that the Department's consequent view of the affairs of the industry from a perspective extending beyond straightforward regulation may be a factor in what he described as the 'good job' done by the DHSS. An implicit endorsement of this view came from Mr F. J. Blee (SmithKline Corporation, USA) who expressed concern at the absence of a similar organisational structure in his own country. Professor H. Grabowski, however, questioned whether such an approach could be applied in the United States. Instead he postulated the potential value of a group of medical experts trained in benefit-cost decision making and drawn from both government and other agencies as a suitable replacement for the present system whereby specialist advisers are consulted at the end of the process with little opportunity for seeing the problems in a broader context.

As a final contribution to this part of the debate, Mr R. D. Douglas (Pfizer Europe, Belgium) doubted whether, in a structure with a dual function, a proper synthesis of the two roles is in practice achieved. European experience suggests that officials continue to specialise in single aspects of policy, with little attention being given to the broad view. This results in an uncoordinated patchwork of policies which, in their cumulative effect, adversely affect incentives for the industry.

The other major area of discussion concerned the dangers inherent in failing to define terms accurately. Professor A. H. Beckett (Chelsea College, Britain) emphasised the error of the widespread tendency to regard the terms 'drugs' and 'medicine' as interchangeable and he pointed to pharmaceutical research expenditure and adverse reaction reporting as areas where confusion is inevitable if no distinction is made between the two words.

The same general point was raised in the context of the important difference which exists between accountants and economists in their definition of the rate of return to investment. The lower rate identified by the latter group reflects the consideration that is given to longer-term developments and, in this sense, is particularly relevant to the research-based pharmaceutical industry. It is therefore necessary to be clear about the precise meaning of the figures and the accounting conventions being used. Failure to do so has obvious implications: the control of prices and profits on the basis of inappropriate criteria could jeopardise innovation and hence medicines in the future.

The need for valid comparisons in all matters concerning the pharmaceutical industry was also raised by a number of participants. On a broad level, however, Blee pointed to the absence of suitable industries with which comparison could be made and this stemmed from the unique nature of pharmaceutical products. A specific example of the need to examine like-with-like, given by Dr B. W. Cromie, related to drug potency and formulation when comparing the unit costs of specific drugs. It takes as long and costs as much to develop a new medicine with a daily dose of microgrammes, as it does for a medicine which has a daily dose of many grammes. If they are then priced on the basis of manufacturing cost, the return from one would be many times greater than the other, despite the need to recover the same sum.

At the close the chairman concluded that the problems which had been raised by the speakers and during the afternoon's discussion would have to be overcome if the public demand for innovation and hence better medicines in the year 2000 is to be met.

SESSION III

Present Problems (2)

Chairman *Lord Vaizey*

The argument which has come from the discussions that we have had so far is of course complex, but it boils down to a fairly simple set of propositions in some respects, that the growing public concern with safety and also the growing concern with profit margins by various government agencies has led to increasing regulation of the pharmaceutical industry which, by raising costs of research and testing, has substantially reduced the rate of innovation. To this proposition, which prima facie seems to be a probable hypothesis, really two alternatives have been offered: the first is that it is just not true. Governments have pointed to the fact that the flow of new drugs seems to be no less now than it was before. Alternatively, a rather more complex and sophisticated reply is that in any case pharmaceuticals have not been primarily responsible for the immense improvement in public health which has been seen in this century, and that doctors and other medical scientists have increasingly come to the view that most health problems are best dealt with by adopting a healthier mode of life, and that medical intervention, if anything, should be minimised.

Obviously, I have stated the view very simplistically, but I think that was the general tenor of the argument that we had yesterday, and it is a very important and interesting argument, not only for us as individuals but for us as citizens, when we consider the way in which health care should be organised in our country.

There is a third hypothesis, in which I am particularly interested, whether or not the inventive capacity of western man is not generally diminishing; whether we are not seeing some profound change in the scientific imagination which has so dominated western thought for the last three centuries – but that is probably a subject for another seminar on another occasion.

Economic competition in pharmaceuticals

W Duncan Reekie
Lecturer in Business Economics University of Edinburgh
Visiting Professor of Economics Pace University, New York City

1 Introduction

Pharmaceutical prices are viewed with concern in most countries. Some people even question whether any industry should be allowed to earn profits from the sick. In Britain, where most drugs are paid for by government, the Department of Health and Social Security (DHSS) works within somewhat less but still restrictive guidelines. The advice given to all Departmental purchasers is that 'suppliers of goods to Government must earn the same sort of profits as British industry in general'.[1] Antibiotics, bed linen and toilet paper are regarded as equally meritorious. A third view is that because of the high degree of risk and uncertainty facing the pharmaceutical industry in its Research and Development (R and D) and because it is technically highly efficient then profits should be well above the industrial norm in order to reward these factors in the past and induce their continuation in the future.

Which of these opinions is correct cannot be settled by verbal debate. 'Reasonable profits' exist when they are sufficiently large to call forth the resources to produce the goods and services consumers want in the quantities and qualities they prefer and at the prices they are prepared to pay. Profits above or below this level are unreasonable or inadequate. The 'correct' level will vary industry by industry and period by period according to varying conditions of tastes, preferences, innovation and technology, and risk and uncertainty.

If there is a rationale for the existence of price controls over drugs then it must lie in the belief that unregulated market forces are failing to bring about price levels which would result in reasonable profits. This belief may exist because on the demand side of the market doctors (who select drugs) do not pay for the products they prescribe; and patients either do not pay or regard the medicines as so essential that they (and the doctors) are price indifferent. Or it may be because, on the supply side of the market, firms are believed to have the ability persistently to price their products above 'reasonable' levels since competitive market rivalry is absent.

Certainly there is almost universal concern over the levels of pharmaceutical prices and profits. Moreover this unease is present in countries with widely differing health care systems.

For example, in Britain, where nearly 100 per cent of all drugs are provided at a zero or nominal price to the patient, the government controls prices through the Pharmaceutical Price Regulation Scheme (PPRS). In the USA price regulation is less overt but is prevalent nonetheless. There

some 85 per cent[2] of all drugs by value are paid for directly by the patient. In the remaining government funded sector doctors are discouraged or prohibited from choosing drugs priced above a given level. The mechanism employed by the Department of Health, Education and Welfare (HEW) is the MAC (Maximum Allowable Cost) legislation. In general MAC sets limits on the amount HEW will reimburse for drugs having mutliple sources of supply. In Holland, which falls between the predominantly private US system and the totally socialist British system, 70 per cent of the population come under the 'sick fund' provisions. Whether a medicine can be provided without charge under the sick fund arrangements depends on the Central Medical Pharmaceutical Committee (CMPC). The CMPC provides advice to the sick fund administrators and this 'advice', although without *de jure* powers is generally accepted as an instruction *de facto*.[3]

If the case for price control in the industry is indeed rational, then it is based on the presence of some form of monopoly power derived from peculiarities on either the demand or the supply side of the market. In the latter instance monopoly can be measured by yardsticks such as concentration ratios or ease of industry entry. The height of entry barriers is probably the more valuable as a criterion. If an industry is earning profits of an unreasonable level and if barriers to entry are absent, then new firms will come into that industry and, in order to gain sales, will price at levels below the going rate. In the long run this will reduce both prices and profits to normal competitive levels. This in turn will be reflected on the demand side of the market by changes in demand elasticity (or price sensitivity). The greater the price sensitivity for the products in a given market the more competitive that market is.

The following sections examine the supply and demand sides of the industry in the three countries already mentioned: Holland, the USA and Great Britain. In conclusion, an attempt will be made to assess the comparative data and its implications for regulation.

2 Competition in creativity

There are very few industries in which a market can be lost as quickly as in pharmaceuticals. A six-year study by myself stretching from January 1972 to December 1977 in Holland showed that only one firm in the top twenty-five firms retained its original ranking by sales revenue. Even that firm suffered a market-share decline from 7.01 per cent to 5.34 per cent of the Dutch market. The top three and top five firms held, in 1972, 22.64 per cent and 31.44 per cent of the market. By 1977, these same firms accounted for 16.94 per cent and 26.14 per cent respectively. In the drug industry 'the top is a very slippery place'.

More detailed analysis of the Dutch market produces further supporting evidence.[4] In Britain, Michael Cooper's well known studies for the middle 1960s[5] and in America Douglas Cocks'[6] work for the late 1960s and early 1970s strengthen, by repetition of outcome, the conclusion drawn above. This conclusion, that competitive entry is frequent and effective is the same irrespective of which of many indices is used. (For example, numbers of new firms, growth of new firms, rank correlation coefficients, or the Hymer-Pashigian index.[4,5])

The inability of firms to dominate the market and the risks attendent with frequent new challenges by others is the natural outcome of competition by innovation. It is the result of a high level of R and D. What impact, if any, does this have on price?

3 Entry and price competition

In the USA, David Schwartzman carried out a study of price levels for products which are multi-source. When patents expire, products are no longer unique to their original innovator and a few licensed competitors who pay royalties to the patentee. Instead, any manufacturer who cares to do so can enter the market and produce and sell chemical equivalents. The principal market in which patent protection for many large selling drugs has disappeared has been antibiotics. That market, according to Schwartzman, 'became a jungle', with prices falling to levels which were well below those at the beginning of the 1960s.[6]

Even in the case of products where patent protection still existed and licensees entered the market, entrants generally adopted a lower price than existing firms. This competitive pressure tended to force down the prices of existing producers of the drug. In the case of ampicillin, for example, Schwartzman found that only one product (Amcil) failed to enter the market at a lower price than the leading product (Polycillin), and also lower than the products which had entered earlier.

Schwartzman also discovered that although some firms 'with larger market shares tended to hold back (from retaliatory price cutting) *in each case* they eventually were forced to cut their prices due to losses in their shares of the market'.[7]

Also in the USA, Lester Telser[8] covered a similar time period to that of Schwartzman (1963–72) but examined virtually the entire industry and did not restrict himself to antibiotics nor to multi-source drugs. Entry, as defined by Telser, was the proportion of sales (in dollars) in 1972 in a therapeutic category by firms that were absent from the category in 1963 or some other initial specified date. Thus the measure was closely related to successful or net entry.

Telser's main conclusion was that prices tend to fall in response to entry. Entry itself was an increasing function of sales growth, market size, and promotional intensity. There was a statistically significant and inverse relationship between the rate of change of prices and industry entry.

Entry appears to be important as a determinant of price in the USA, as illustrated by both Schwartzman and Telser. It is therefore worth recording the results of a British study which showed that in 1966 more than one-third of the firms in the UK industry (26 firms out of 71) had entered since 1950[9] and accounted for over 20 per cent of the industry's sales by 1966. This analysis also showed that, except for the newest entrants which had not had time to establish themselves and grow, there was no indication that new entrants since 1950 were typically smaller firms than those established in earlier years. It appears that unlike more traditional industries, both rapid relative and absolute growth can occur soon after entry.

4 Price: Quality competition in the UK

In a recent study of pricing behaviour in the UK industry,[10] I examined almost all New Chemical Entities (NCEs) launched onto the market between 1962 and 1970. The NCEs had previously been ranked on a '1' to '5' scale in descending order of incremental clinical significance at date of introduction. This information was compared with their respective daily dosage costs (relative to close substitutes) and with their levels of achieved sales in their first few years of life.

Approximately one-third of all the innovations were introduced at lower prices that those of leading available substitutes. A high initial price was employed more frequently for major than for minor innovations. But where a low price was adopted for an innovation (of any rank) this was significantly related to a likelihood that competition, in the form of a superseding chemical entity, would emerge in the near future.

In other words, the pricing behaviour of the industry was not inconsistent with what one would anticipate if firms *did* believe that doctors took price into consideration when writing prescriptions. It was not inconsistent with what one would expect if firms *did* consider rivals' responses when setting their own price.

I argued that the results were possibly *not* due to the British government's Voluntary Price Regulation Scheme since the version of the VPRS which existed during the study provided firms with a 'freedom period' during which they could pitch their prices at their own chosen levels. I went on to say that this assertion would be worth testing. By comparing, for example, what had happened in the UK with what had happened in a market subject to much less price regulation than the monopolistic British situation. The logical follow-on study was thus carried out in America.

5 Price: Quality competition in the USA

Four basic questions were posed in the American Study:[11]

1 Are NCE prices determined exclusively by forces on the *supply* side of the market (such as advertising), or does demand have a role?
2 Once determined do NCE prices converge towards some competitive mean, or can they remain monopolistically high?
3 Do NCEs prompt price cuts in competing products? Or can competitors maintain prices even in the face of innovation?
4 Are doctors price sensitive? What is the price elasticity of demand for NCEs (a) at launch? and (b) through the life cycle?

In the USA a longer data series (1958–75) was used, and the qualitative ratings were those devised by the Food and Drug Administration. Over 40 per cent of the NCEs were introduced at lower prices than leading substitutes. Those that were priced at high levels relative to competitors again tended to be innovations providing 'important therapeutic gains'. This fits within the behaviour pattern one would expect from simple price theory. Firms *can* charge a higher price in those cases where consumers are willing to pay that price. Consumers *will* pay if the innovation is relatively more productive than alternative products. Minor variants, conversely, can only penetrate a market if their price is below that of existing rivals.

Given the Sylos postulate, their demand curve is that part of the market demand curve to the right of ruling price.

More detailed analysis of the data answered the other three questions. NCE prices tend to fall over time; existing products tend to be cut in price in the face of innovation as firms attempt to gain a price advantage where a quality advantage has been lost; and that price elasticity of demand (a) either increases as products mature (and so are subject to competition from later drugs); and/or (b) is lower initially the more important is the therapeutic gain represented by the NCE (see Tables 1 and 2).

It could be argued, however, that price competition is relatively *more* likely in the USA than in a country like Britain. In the USA, doctors have long been aware that different patients have different incomes and so vary in their ability to pay. This is reflected in their use of price discrimination[12] and their levying of varying fees for the same treatment. It seems unlikely that such doctors will be price sensitive agents on behalf of their patients' needs for some parts of the total health care 'package' they provide but not for others (namely drugs). If we bear in mind that the doctor will be assessing the cost effectiveness of a drug, given the patient's total socio-medical needs, it does seem probable that on occasion – if not many occasions – he will deliberately prescribe cheaper and/or older and/or less

TABLE 1 **Price statistics relating to all new chemical entities launched in the United States drug market (1958–75)**

	Year 1	Year 2	Year 3	Year 4
Mean	1·618	1·519	1·345	1·287
Maximum	15·516	11·969	5·128	5·449
n	185	175	163	146
Variance	3·577	2·022	0·709	0·500
Variance Ratios				
Years 1–2		1·769*		
Years 1–3			5·045*	
Years 1–4				7·154*
Coefficient of variation	1·169	0·936	0·626	0·549

*Statistically significant at the 1 per cent level.

TABLE 2 **Demand elasticities for NCEs in the US market analysed by FDA rating and product maturity**

	FDA rating	
	Important therapeutic gain	*Modest therapeutic gain*
Year 1	1·03	1·11
Year 2	1·65	2·68
Year 3	1·30	1·79
Year 4	ns	2·83

ns=not significant.

effective or less potent and/or generic, unbranded products. Also there is the additional price constraint in the USA that the patient can shop around for the cheapest retail pharmacy to fill his prescription. Patient price-awareness of this sort, will, *a priori* also influence prescriber price-consciousness. When the disease is one which required continuous repeat prescription therapy (eg rheumatism) as opposed to a single short-period regimen (eg infections) this effect, *a fortiori*, will be enhanced.

An additional qualification is that in both the British and American studies, the quality ratings which were used had been devised retrospectively by British or American clinical and pharmacological experts who were already aware (at least approximately) of each product's commercial performance. The 'experts' thus might have been influenced, however objective they tried to be, in their rating evaluations by the market success of the product. In short, the association discovered between 'quality and doctor' acceptance might well be the reverse of the causal relationship attributed to it in these two investigations. One way to isolate this factor is to replicate the exercise in a third market or country where the commercial performance of the products was not known to the panel of experts who awarded the ratings. This was done in Holland for the period 1970–77 using the American FDA ratings.

6 Price: Quality competition in the Netherlands[4]

In Holland the data again indicated that only highly rated products tend to achieve doctor acceptance irrespective of price. Statistics similar to Table 1 for the American industry showed that NCE prices fall over time, while values like those in Table 2 provided further corroboration that doctor price sensitivity increases as products and subsequent competition and/or is lower the more important is the incremental therapeutic gain represented by the NCE.

Conclusions

None of our discussions nor the work reported on in the preceeding pages provides definitive conclusions. Nonetheless, collectively, the various empirical investigations provide considerable insights into how pharmaceutical prices should be defined, how and when doctors are price-sensitive and, in consequence, in what direction regulatory activity should be channelled with a view to improving the industry's economic performance.

Price is not cash price. The real price of a pharmaceutical must be modified by the quality of the product. Like any other good or service, a pharmaceutical's selling price is measured by the amount of other goods and services the customer must forego in order to purchase the characteristics of the drug. For example, if an existing drug requires four pills per day to be consumed for one week at 10p per pill, with the additional requirement of confinement to bed, then the real price of that drug to the consumer is £2.80 ($7 \times 4 \times 10$p) *plus* the week's wages he has foregone by being confined to bed. (Alternatively if the total cost is borne by society through socialised medicine and health insurance, the social cost is the

same, namely £2.80 plus the value of goods and services the patient could have produced had he been at work.) On the other hand, if an alternative drug becomes available at £2 per pill, to be consumed at a rate of one pill per day for three days with only three-day home confinement, then the real cost to the consumer is £6 plus only the proportion of one week's wages represented by three day's loss of work.

The new drug costs £6 for a full treatment, the first £2.80. But the second drug is by far the more competitive in terms of real price. The second drug's real price is £6 plus three days wages (for a five-day week), say £66; the first drug's price is £102.80 (for a five-day week for a patient normally earning £20 per day. The second drug has lowered the price of treatment by £36.80. That is price competition in the real meaning of the phrase.*

In the simple example just described, the new drug lowered the real price of treatment. If competition works we would expect the price of the existing drug to fall to combat the price of advantage of the innovation. Since the quality of the existing product cannot be changed the alteration must occur in its cash price. The evidence presented above from a variety of studies on both sides of the Atlantic suggests that this is precisely what happens. As NCEs are introduced onto the market the cash prices of existing products are pushed down by competitive forces, and the elasticity of demand for existing products increases. Doctors tend to continue prescribing older products only if they are reduced in cash price and their real price disadvantage relative to better quality products is minimized.

Similarly we have seen from the evidence that new drugs which do not reduce the real price of treatment *via* improved therapeutic quality, must, in order to enter the market, reduce the real price of treatment *via* a lower cash price. There is little or no evidence on the demand side of the drug market to suggest that doctors are unaware of real price differentials. Little support has been found for the view that drug prices need to be regulated by government because demand is highly inelastic.

Market entry, by innovations from existing drug firms, or by innovations from firms new to the industry, has played a major part in reducing real and monetary drug prices over the years. Thus on the supply side of the drug market there is again little to suggest that prices are at levels relative to marginal cost which indicates the possession of monopoly power by drug firms, and so the need for price regulation by government. If entry (of either kind) is deemed to be declining, however, this situation may change. The first task of a government agency then, should not be to control prices but to ensure that entry barriers have not been raised either by existing firms in the industry or by governmental controls favouring existing firms at the expense of potential new entrants. (Such as those proposed or already in force on R and D and promotional activity.)

The welfare implications indicated by the studies of demand elasticities is that the industry is *not* perfectly competitive in the sense of static micro-theory. Demand elasticities are *not* infinite. Monopoly rents *are* reaped. But these rents are the sources of funds for the research and development which provide future innovations. Schankerman has shown that it may be

*To paraphrase a comment made to me by Yale Brozen.

socially optimal for this difference between price and marginal cost (a difference which funds R and D) to be greatest where demand elasticity is least.[13] Our results indicate that the industry is behaving in the way Schankerman suggests is optimal. Moreover, the rent reaped is transitory. Prices are eroded over time and converge towards some variant of the competitive norm. This implies a dynamic process of the kind outlined by Cocks.[14]

There are reasons why this process probably does *not* result in an overall resource misallocation.

In brief, many firms are possibly already operating at P=MC for their marginal products. In addition, the marginal consumer possibly buys a product from a firm with price close to marginal cost. This speculation, bolstered by the fact that the economic rate of return for the industry, as opposed to the accounting rate of return, is reportedly very similar to that for all other manufacturing industries,[15] leads me to wonder if we are not studying the wrong phenomena. Maybe we should be directing our attention away from price and profit studies. Maybe we should instead be attempting to ascertain what the theoretical margin of profits *above* the industrial norm should be if we believe it necessary to continue the inducement of innovative activity.

REFERENCES

1 Reported from a speech by Alan Beard, Controller of Supply in the DHSS, to the Pharmaceutical Manufacturers' Association of the USA. *ABPI News* September, 1977.

2 Reekie W Duncan and Weber Michael H. *Profits, Politics and Drugs*. Macmillan, 1978, p 117.

3 *Pricing in the Pharmaceutical Industry*. Nefarma, 1978, p 19.

4 Reekie W Duncan. Unpublished data.

5 Hymer S and Pashigian P. Turnover of firms as a measure of market behaviour. *Review of Economics and Statistics*, 1962.

6 Schwartzman David. *Innovation in the Pharmaceutical Industry*. Johns Hopkins, 1977, p 251.

7 *Ibid*, p 298.

8 Telser Lester. 'The supply response to shifting demand in the ethical Pharmaceutical Industry', in R B Helms (ed), *Drug Development and Marketing*, American Enterprise Institute, 1975.

9 Reekie W Duncan. 'Barriers to entry and competition', in G Teeling-Smith (ed), *Economics and Innovation in the Pharmaceutical Industry*. Office of Health Economics, 1969, p 3.

10 Reekie W Duncan. *Pricing New Pharmaceutical Products*, Croom-Helm, 1978.

11 Reekie W Duncan. 'Price and Quality Competition in the United States Drug Industry'. *Journal of Industrial Economics*, 1978.

12 Kessels Reuben A. 'Price Discrimination in Medicine'. *Journal of Law and Economics*, 1958.

13 Schankerman Mark A. 'Common Costs in Pharmaceutical Research and Development: Implications for Direct Price Regulation', in Samuel A Mitchell and Emery A Link (eds), *Impact of Public Policy on Drug Innovation and Pricing* (American University Press, 1976) pp 3–45.

14 Cocks Douglas C. 'Product Innovation and the Dynamic Elements of Competition in the Ethical Pharmaceutical Industry', in Robert B Helms (ed) *Drug Development and Marketing* (American Enterprise Institute, 1975) pp 225–54.

15 Clarkson K. *Intangible Capital and Rates of Return* (Washington, DC: American Enterprise Institute for Public Policy Research, 1977).

Emerging trends and future prospects in the less developed countries

Sanjaya Lall
Institute of Economics and Statistics, Oxford University

1 Introduction

This paper reviews some problems facing less-developed countries (LDCs) in providing adequate medication to their populations; it addresses itself, in particular, to the role that the large, research-based, multinational pharmaceutical companies (MNCs) can play in fulfilling LDCs' objectives. Only market economy (non-socialist) less-developed countries are considered here.

The medicinal needs (and thus the appropriate set of policies towards drug producers) of the rich industrialised countries differ from those of poor developing countries. While both groups are essentially concerned with reconciling the desire to hold down pharmaceutical prices with the provision of sufficient economic incentives to drug producers, the richer countries are mainly concerned with sustaining increasingly expensive innovation while injecting a stronger element of price competition. The LDCs, on the other hand, are primarily concerned with obtaining a relatively few, mostly (but not exclusively) established, drugs at the lowest possible prices while promoting local drug manufacture. There are, of course, common threads running through the recent attempts of both groups – the control of the marketing and information-dissemination systems, the promotion of generic names, the encouragement of R and D in specific areas of interest to the countries concerned, expansion of exports, and so on – but in general it seems fair to say that the balance of objectives of rich and poor countries is, and should be, rather different.

There is a great deal of difference between individual LDCs, according to their income levels, socio-political structures and levels of industrial development. To lump them all together involves heroic simplification, but as in this paper we cannot hope to do justice to their diversity, we shall concentrate on their commonly shared ground.

The pharmaceutical industry is one of the most tightly controlled and heavily scrutinised of all industries in developed as well as less-developed countries. The process of regulation in one cannot be separated from that in another. On the contrary, there seems to be a growing tendency for the regulatory authorities in different countries to observe, and sometimes imitate, what others are doing. This tendency is most marked among the more developed countries. The LDCs have generally tended to formulate their policies in relative isolation, though there seems to be a growing awareness on their part of major changes taking place elsewhere.

Despite a few attempts by individual LDCs to drastically change the system of drug provision (Pakistan and Sri Lanka, for instance), the most

far-reaching changes are taking place in the developed countries. The emergence of substitution laws to encourage generic prescribing based on careful evaluation of quality and bioequivalence, of strict checks on new drug introduction based on safety and efficacy, of price controls based on discrimination between innovation and imitation and on prices charged in other markets, of alternative channels of information-provision to the medical profession as well as a tighter vetting of promotional material – all these measures point to a gradual but significant restructuring of the pharmaceutical industry as compared to only a decade or so ago, and all of them are being undertaken in the developed countries. The LDCs are following a more erratic, but on the whole slower, path of change, but their course is undoubtedly influenced by the policies of developed countries. In the long run, the 'international demonstration effect' of regulation in the latter is likely to be very powerful. These linkages, again, cannot be discussed in detail here, but the broader context of regulation should be borne in mind.

The issues facing LDCs can be conveniently organised under four headings – imports, domestic production, marketing and innovation – which cover most of the important policy areas currently under discussion. It is difficult to make a firm distinction between these four groups, and some repetition of particular problems is inevitable. Nevertheless, a grouping of this sort is useful for purposes of discussion, and we may briefly consider, for each of them the present problems, possible solutions and the role of MNCs in these solutions.

II Imports

A few large LDCs in relatively advanced stages of industrialisation – India, Argentina, Brazil and Mexico – have developed the capability to produce a wide range of pharmaceuticals locally from the first stages. Most others continue to be heavily dependent on imports, in the main from the large transnational companies. The smallest and least industrialised countries import practically all requirements in finished form. The others import pharmaceutical chemicals and bulk chemicals of various kinds to formulate and package locally. The most advanced LDCs import only those bulk chemicals for which they have not yet established local production: these depend on MNCs partly for the supply of these (generally very new and sophisticated) chemicals and partly for the establishment of local manufacturing facilities by direct investment or sales of technology.

Recent concern in this area of imports of products (technology is considered later) has centred around two sets of issues: first, the number of products imported, and the need for an 'essential drug list'; and, second, the pricing of pharmaceutical products.

The need for a reduced and rationalised list of 'essential drugs' has been at the forefront of much debate at the World Health Organisation. The idea is not new: it is based, in essence, on the concept of formularies used in most hospitals. As a device for controlling *national* drug supplies, however, it is more recent. A few LDC governments and institutions (in India, Sri Lanka, and Brazil, for instance) have started, or planned, the introduction of reduced lists of drugs within the last decade. In the last year or so, the international organisations concerned with drug provision (WHO,

UNCTAD and UNIDO) have come out strongly in favour of such lists, and some suggested lists, with about 200–300 drugs, have actually been prepared by international panels of experts.

There is some confusion about what such a list contains.[1] Some view it as a list of 'basic drugs' which will meet the most pressing health needs of LDCs: in such a case, only about a hundred drugs will serve to meet 80–90 per cent of the most commonly encountered ailments, and the rest will be met by an unregulated market. Others view it as a 'rationalised list' wherein the entire market for drugs is controlled, and the numbers of drugs permitted is greatly reduced in comparison to what a free market would provide. I prefer the second definition, and shall confine myself to it. The 'list' applies, of course, to local production as well as imports.

The case for an essential drug list must rest on some perceived imperfection in the free market mechanism which prevents it from providing medicines of appropriate quality and quantity at appropriate cost and with appropriate information. The facts that the market provides a large number of alternative drugs, or that it contains price differences for identical products, which can be reduced by official intervention, are not as such justifications for an essential drug list. After all, variations on a given product are an indication of active competition, and such competition may lead to prices which are socially acceptable. Even if prices could be further reduced by government policy, this may be accomplished by price control, by promoting more competition or by bargaining with the producers. There is no need to reduce the extent of choice which the market offers, unless additional arguments are advanced.

Such arguments can, in fact, be advanced. First, an unregulated market can provide drugs which are ineffective (in the FDA sense) or which are unacceptably toxic. Second, it can provide drugs which are effective, but which cost too much (in given countries) in terms of the advance they offer over alternative older forms of treatment. Third, the proliferation of drugs creates the need for a powerful promotional mechanism which, while it may be a very effective means of transmitting information, may cost too much by comparison with alternative information systems, and may not provide information which is optimal in terms of rational prescribing practice. Sufficient evidence and concern exist on all these counts, in rich and poor countries alike, to bear out the need for some action on the part of LDCs. How far-reaching and drastic this action need be is another matter.

The essential drug list provides a relatively straightforward means of tackling these problems, although several other instruments also exist for resolving them. Its main attraction is that it combines the functions of (a) a drug screening and registration authority, (b) a centralized buying and price control office and (c) a generic-promotion and information regulation agency. Some of these points will be touched on later, but the apparent theoretical merits of an essential list should not blind us to its practical problems: first, it leaves a great deal to the discretion, efficiency and knowledge of the officials responsible for drawing up essential lists; second, it involves major problems of quality and bioequivalence when the sources of supply are selected; third, it entails several difficulties in pricing drugs, especially when genuine innovations are involved; and,

finally, it has to institute an information-dissemination system which is as effective as the one it seeks to replace.

Only the actual experience of implementing essential lists in different countries can enable us to gauge whether the benefits balance out the costs. The limited (and not unmixed) experience of Sri Lanka and *a priori* considerations of conditions in poor countries, may lead us to come out in their favour in principle. There are, however, two strong forces which oppose the use of rationalised drug lists: the drug industry, both locally and foreign-owned[2] and the medical profession.[3] In view of such opposition, it appears doubtful that the experiment will be repeated in many parts of the Third World, at least in as comprehensive a form as envisaged in the theoretical concept of the essential list.

What is much more likely is that some form of compromise between the free market and essential lists will be attempted. The Central do Medicamentos (CEME) scheme in Brazil, providing cheap medicines to the poor in the north-east, is one such compromise which has already been in effect for some years. CEME applies its essential list to a restricted market, and the private sector collaborates by providing it with drugs at preferential prices (CEME also manufactures some drugs) as long as the richer markets are left unaffected. The German-Swiss MNC-sponsored scheme to provide a few 'basic drugs' at cost to the poorest of the LDCs, in return for unregulated markets in new drugs, is a similar compromise. If combined with a stringent drug registration scheme (such as has been used by Sweden, and is increasingly being used by other developed countries), which rules out ineffective and toxic drugs, and a policy of encouraging price competition (by promoting generic products) with stricter control of drug promotion (as is common in the rich countries) such compromises may well be able to provide most of the benefits of essential drug schemes without paying some of the attendant costs.

Compromises have their own problems, of course. The German-Swiss scheme, for instance, is equivalent to setting preferential prices on some products. Many MNCs are resistant to the idea of setting such preferential prices for LDCs, especially when developed country authorities keep a careful watch on prices internationally and when anti-trust issues (especially in the United States) may be involved. On the other hand, it may be argued that MNCs have little choice over the long term about reducing prices for LDCs. With the increase in generic competition in several essential drugs and with the MNCs' own entry into generic markets (especially in the United States), the forces which have traditionally enabled them to maintain much higher prices for their branded products are being weakened.[4] The bioequivalence issue is better understood now.[5] United States efficacy test data may soon be internationally available. Several good quality generic suppliers exist, in advanced and developing countries. Governments are increasingly aware of the possibilities and rewards of 'shopping around'. Several essential drugs are now out of patent. A dual price structure – between patented and multi-source drugs – may emerge simply from market forces. In the future, therefore, MNCs may well be *forced* to reduce prices of essential drugs to LDCs: it may be much more politic to anticipate such a trend and win goodwill by negotiating a broad-based scheme of providing as many drugs as possible (ie, excluding major

innovations) to LDCs at lower prices. The main barrier to such a scheme would be the authorities of the developed countries, but they are pressing ahead with their own schemes for reducing prices of multi-source drugs in any case, and may respond to a concerted appeal from the Third World for an extension of such efforts to international markets.

This still leaves untouched the problem of pricing innovative drugs in LDCs. If the process of pharmaceutical R and D is to continue, and there is no doubt that every responsible health authority would want it to, the prices of new drugs must reflect the high cost and risk of doing so. The question is what share of the cost should be borne by the LDCs. The innovating firms distribute the cost (though not always evenly) over the entire market by the prices they set, and in a sense this is 'fair' because every consumer pays for the extra benefit (assuming that it *is* extra) by the premiums charged over older drugs. It may, on the other hand, be argued that LDCs should pay less for innovations that were aimed primarily at developed country markets (rich man's drugs) than for those aimed at their own markets (poor man's drugs).[6] However, this argument assumes that the flow of innovations in rich man's drugs would not be affected by the loss of premiums in LDC markets, ie, that the 'opportunity cost' in terms of future innovation of cutting the contribution to R and D would, in other words, be low or nil. Such an assumption may well be unjustified. Given the rising pressures on innovation in the developed countries, a further cut in premiums by the LDCs may reduce investments in R and D even in rich man's drugs. Unfortunately, there is insufficient hard evidence to allow an evaluation of this situation.

Even if LDCs could cut premiums on rich man's drugs without affecting innovation, it is difficult to envisage how such a pricing system could be made to work in practice without a comprehensive plan organised on an international basis. There would be immense problems in allocating drugs to different categories, in calculating correct premia, in getting the approval of the developed country governments, and of course, in winning even a minor consent of the firms concerned. The most likely outcome is one which only differentiates new from multi-source drugs, and treats all new drugs equally – which, in other words, maintains the present system of financing innovation.

A brief word about another sort of pricing problem: that of transfer prices set by MNCs on intra-firm transactions. After the initial flurry of interest and activity in the Andean Group countries in transfer pricing problems in the pharmaceutical industry, the main measures to check it have in fact been initiated by the developed countries. The United States and Canada are starting joint audits of several MNCs (including many drug companies), and the fiscal authorities of various European countries are trying to coordinate their activities to check price manipulations by MNCs. Many developing countries seem to do relatively little to check transfer prices; and those that do tend to use simple criteria to assign reference prices. In general they pay insufficient attention to the R and D costs incurred by MNCs. Clearly, what is needed in the longer term is greater 'transparency' and consistency on the part of MNCs as far as their pricing strategies in different countries are concerned, and a greater understanding on the part of LDCs about the true cost of products based on

heavy R and D investments. If this does come about, this highly charged issue might be defused, and reduced to a simple matter of regular negotiations between fiscal authorities and MNCs.

III Local Production

The development of local industry in LDCs requires in part the attraction of MNC investment and in part the development of indigenous enterprises. Pharmaceutical MNCs have been among the first to set up production facilities in LDCs, though most of them have been confined to relatively simple and small-scale formulation and packaging operations. With the exception of a few countries which have established local industry or large-scale public investments in this sector, MNCs account for three-quarters or more of drug manufacturing in LDCs.

The future development of manufacturing activity in the larger LDCs will require one or both of two things – greater investment by MNCs in the production of bulk chemicals in LDCs; and a greater transfer of technology by them to indigenous enterprises for such production. While both can proceed together, there is clearly an area of potential conflict. MNCs may wish to exploit a particular technology by setting up their own facilities, while a host country may wish to purchase a licence and exploit it in a locally-owned facility. The exact nature of the conflict will depend on political and economic forces in each country, but clearly in places like India considerable friction does exist on this score. A recent example is the production of chloroquin phosphate: MNCs wish to expand their own production of this drug in India, while the IDPL (a public sector firm) wishes to purchase the technology outright. The conflict has been resolved by the intervention of UNIDO, which has purchased the technology for a lump-sum from an east European country and is preparing to hand it over to India.

With the growing desire of several more industrialized LDCs to promote the development of indigenous enterprise, we may expect a combination of the following outcomes in the future:

- more demands on MNCs to sell technology outright;
- the dilution of equity of MNCs to the extent that local interests gain effective control over large areas of operation;
- the growing purchase of technology by LDCs from Eastern Europe and also, where possible, from smaller firms in the developed countries;[7]
- the development of local technologies to imitate, adapt and improve on foreign technologies;
- the transfer of simpler technologies from the more advanced to the less advanced LDCs;[8] and
- some form of cooperative research into local illnesses and locally available plants and herbs.[9]

A certain division of activity may be expected to emerge between the foreign and indigenous sectors in the larger LDCs, with the former specialising in more complex and capital-intensive forms of production.[10] At the moment, however, MNCs are reluctant to set up the production of bulk chemicals in developing areas, and do so only under severe pressure from the host government. A more far-sighted attitude would be to assess how dynamic comparative advantage between the developed and less deve-

loped ones will evolve over the next two decades, and to plan accordingly. This would involve relinquishing the control over certain technologies to LDC firms, and exploiting others by investing in LDCs. As with many other industries which find that certain processes are cheaper to work in LDCs, the international pharmaceutical industry may also find it economical to relocate many of its facilities there and use them to service their world markets. LDC governments welcome investments that are export-orientated, and a strategy of using LDCs as export bases would serve the interests of both the host countries and the MNCs. (Beecham have set up an export facility in Singapore, and several MNCs export from their affiliates in India.) The economic costs and benefits of extending such relocation need to be explored on both sides, and adequate measures to promote and protect it must also be investigated.

In sum, therefore, MNCs can promote local industrialisation in LDCs by anticipating a changing division of labour on two fronts: between them and indigenous firms, and between their investments in rich and in poor countries. This would entail on the MNCs' part a more liberal stance on transfer of technology and also a more positive policy on establishing bulk drug production in LDCs. It would entail, on the LDCs' part, firmer and clearer assurance to the foreign enterprise that both technology and direct-investment deals would be profitable and fair, and that property rights on new technology exploited by them would be respected. In countries like India and Argentina, the interpretation of patent laws often tends to support local imitators of patented technology. Given the growing capabilities of local firms, some transfer of technology to them has to be accepted, even for patented products or processes, by MNCs. In return for this, however, the government should strengthen protection for technologies which MNCs have invested in within their economies, and should extend patents for innovations of specific interest to them. The present system, with its potential for conflict of interest, has the worst of both worlds: it does not provide a sufficient deterrent to widespread imitation of new technology, and it inhibits a smoother transfer of technology from MNCs to LDC enterprises. A much better arrangement would be to prevent imitation in specified areas and to agree on a speedy transfer of technology in others, in accordance with the comparative advantage of the relative sets of enterprises.

IV Marketing

The issues facing LDCs in the area of marketing medicines revolve around the well-known and oft-debated problems of brand/generic names; the optimum way to inform doctors and achieve rational drug use; and the information content of package inserts and labels of drugs sold in LDCs.

There is little to add here which is new, so I shall be very brief. The general desirability of promoting generic prescribing is widely argued by health authorities all over the world. What is emerging more recently is the complexity of the task of achieving a change from brand to generic drugs. In LDCs in particular, the problems of quality, bioequivalence, doctor-acceptance and patient-acceptance, are all far more severe than in the advanced countries, and hasty and ill-planned moves like the Pakistani abolition of brand names have only served to retard genuine progress.

MNCs have been consistently and bitterly opposed to policies to promote generic drugs, though they have, as noted earlier, successfully entered these markets with their own branded generics. The long and continuing battle between the FDA and PMA on this subject makes fascinating reading, as the industry is forced to retreat from one line of defence to the next: LDCs would do well to carefully study the arguments on both sides before launching any major changes.

The control of the cost and contents of drug industry promotion is again a problem which requires very careful scrutiny and very gradual change. There is, to my mind, little doubt that the present method of information, effective though it is, is wasteful for poor countries. At the moment, however, there are few realistic prospects of replacing it with an alternative system run by the government, especially in large LDCs with substantial domestic production and very widespread markets. It would seem more sensible to aim for cost reductions and information control along the lines followed in the United Kingdom and other developed countries, leaving the existing structure essentially intact. If essential drug lists and generic prescribing are brought into operation, however, the normal commercial incentives to private firms to promote their products will be much reduced, and the government may be forced to step in with a comprehensive information, representation and sampling system.

As for drug labelling, there are three possible (complementary) courses which may be followed (or are already being followed) to counter the problem of exaggerated claims and suppressed counter-indications which has earned MNCs a bad name in LDCs. First, the LDCs themselves may adopt stricter standards in their regulatory policies, perhaps drawing upon the standards set in the developed countries. Second, the WHO may act as a central advisory and information collection agency on the appropriate labelling of particular drugs. Third, the MNCs themselves may set international standards which they apply regardless of the laxity of local regulations.[11]

The use of brand names may well be retained for export markets even by countries which seek to phase them out in their domestic markets. Local enterprises, especially smaller ones, in developing countries find the lack of well-known brand names a tremendous handicap in breaking into international markets for formulations. One possible means of breaking down this particular barrier, which has been tried in other industries, is to link a local brand or enterprise name to a well-known MNC name, to familiarise consumers with the former. Mexico and India are two countries actively exploring this technique. It has not, as far as I know, been tried yet for pharmaceuticals, but if it is successful elsewhere, MNCs may well be put under pressure to 'share their names' in export markets.

V Innovation

The WHO cooperative programme with drug manufacturers and researchers to conduct investigations into several tropical diseases has highlighted the need for increased R and D into the specific needs of LDCs that are not being adequately met under the present system.[12] There is hardly a need to argue in support of such programmes. If normal market incentives are insufficient to call forth adequate efforts on the part of research-

based companies, some official or international agency must step in to bear the financial burden. While most of the screening and development work will probably have to be conducted, for reasons of economy, by established R and D intensive MNCs, public laboratories in developed and less developed countries may also make important contributions. The best way of achieving successful innovation for tropical diseases is not clear, and the present situation is, unfortunately, far from promising.

There may be compelling economic reasons to keep basic R and D on tropical diseases centralised in the developed countries. However, it should be feasible to expand research and development into process technology, use of local plants, clinical testing, formulation and packaging techniques, and so on, in the LDCs themselves. Some LDCs, primarily India, are already pushing ahead with their own R and D efforts along these lines. They are also trying to induce local firms to invest in R and D and to attract MNCs to set up research laboratories there. Such efforts are likely to accelerate.[13] Indeed, in view of the vast reservoir of cheap skilled manpower that countries like India can provide, it makes economic sense for MNCs to relocate some research facilities there. A few MNCs have already set up laboratories in India, Brazil and Egypt: more may be in the pipeline.

What is really needed to stimulate private enterprise R and D in developing countries, and to attract MNC R and D facilities, is not so much compulsory requirements laid down by fiat as the offering of a stable and profitable environment for innovative activity. Given their enormous comparative cost advantage, their proven skills and their manufacturing experience, there is little doubt that some LDCs can be highly successful producers of process, and even product, technology in the pharmaceutical field. Once this is perceived, moreover, research-intensive enterprises may well wish to set up R and D facilities without prodding by the host governments. They would, however, require the assurance of pricing, patenting, and other policies which made this commercially viable. Host governments, for their part, would require the assurance that the results of local R and D bore fruit in local industrial investment, increased exports and technological 'spill overs' to indigenous R and D establishments. On the whole, however, there are hopeful signs that LDCs would become significant sources of innovation in the future.

VI Concluding remarks

I have tried in this brief space to review a broad set of problems concerning drug production and provision in LDCs, and to point to the constructive role that pharmaceutical MNCs may play in this respect. There is no doubt that there are several promising areas of mutually beneficial activity. There is, however, also little doubt that there are several sources of potential conflict. A policy of providing essential drugs at the minimum possible cost to poor countries conflicts inherently with the profit-maximisation mechanisms that currently exist for private enterprise. To achieve a workable solution this requires compromise on both sides. The MNCs must recognise that LDCs wish to, and sometimes have the power to, enforce lower prices and promote domestic industrialisation and innovation. The governments of LDCs must in their turn recognise that the cheapening of drugs must not choke off the incentive to invest in innova-

tion, and that all private enterprise activity, with the strictest of controls, must yield acceptable rates of profit. This sort of debate is not confined to LDCs, of course; if anything, it is more heated, and of greater significance, in the richer countries. The situation of the poor countries does, however, require special solutions, and these require careful consideration and much goodwill on *both sides*.

REFERENCES

1 See S Lall, *The Growth of the Pharmaceutical Industry in Developing Countries: Problems and Prospects*, Vienna: United Nations Industrial Development Organisation, 1978 (ID/204), and M Segall, 'Pharmaceuticals and Health Planning in Developing Countries', Institute of Development Studies, University of Sussex, Communication No 119, 1975.

2 In the WHO consultations on Essential Drugs, the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) reflecting in particular the hard line of the United States PMA, has come out strongly against the whole concept of essential lists (SCRIP, various issues).

3 The Sri Lanka experience bears this out, and is analysed in S Lall and S Bibile, 'The Political Economy of Controlling Transnationals: The Pharmaceutical Industry in Sri Lanka, 1972–76', *International Journal of Health Services*, February 1978.

4 The issue of price competition is debated recently by W D Reekie, 'Price and Quality Competition in the United States Drug Industry', *Journal of Industrial Economics*, March 1978, and S Lall, 'Price Competition and the International Pharmaceutical Industry', *Oxford Bulletin of Economics and Statistics*, February 1978.

5 The publication of the New York State's 'list of equivalent drugs' is foreseen as having major implications within the United States and in other countries. See SCRIP, 8 April 1978, p 16–17.

6 I have argued this in my UNIDO (1978) monograph, *op cit.*

7 For evidence of diversification in sources of technology purchased by IDPL (India) see SCRIP, 24 June 1978, p 22. This item also names several out of 30 drugs for which the IDPL has developed its own process technology.

8 Sarabhai Chemicals of India are, for instance, setting up a multi-purpose plant in Cuba under the auspices of UNIDO; the IDPL (a large public sector firm in India) is selling know-how to Afghanistan and several Arab countries. Several private Indian drug companies have set up production affiliates in neighbouring Asian countries.

9 The Central Drug Research Institute in Lucknow, India, undertakes the investigation of medicinal plants for several LDCs. For a recent report on its research activities see SCRIP, 4 March 1978, p 16.

10 Public sector enterprises, as in India, may, however, enter into the 'heavy' parts of the industry where private firms may be reluctant to invest.

11 According to a recent report by Professor Milton Silverman, the MNCs involved in dangerous mislabelling policies in Latin America have now virtually ceased such practices. (SCRIP, 8 July 1978.)

12 See SCRIP, 24 December 1977, p 17.

13 The Indian government may require pharmaceutical MNCs to substantially increase their R and D locally (to about 4 per cent of local sales). At the moment only two or three firms have significant research activity in India. See SCRIP, 8 July 1978, p 24.

The balance of public interest

Gordon R Fryers MD MRCP

Director of Strategic Affairs, Reckitt and Colman

Introduction

As a result of many years spent in the pharmaceutical industry, which more recently includes a much deeper commitment to innovation in other industrial and governmental fields, the writer believes he has gained an unusually wide perspective of its problems. But it goes almost without saying that the views expressed in this paper are personal and do not necessarily represent the policy of Reckitt & Colman or that of the industry in general.

The pharmaceutical industry cannot exist for itself alone; it must serve the public interest as well. The industry possesses characteristics which, under the discipline imposed by competition, enable companies efficiently to develop new chemical molecules, carry out expert pharmacological and biological research and produce high quality medicines. In doing so they aim to serve the public good as well as their own interests.

Yet there is legitimate public concern about some of the industry's activities. This paper will not attempt to deal with all of the problems. Rather it examines two specific areas which have provoked a great deal of debate and disagreement. First, I hope to review some of the changes which are necessary to ensure that the industry continues with its prime innovative role in producing new medicines to meet the many as yet unfulfilled requirements. Such an analysis seems all the more necessary because an increasing number of well-informed observers have begun to question the ability of the industry to go on originating the medicines that mankind still needs.

The second part of the paper deals with the role of the industry in what has been called the Third World, the developing countries. Concern about the role of the research-based pharmaceutical industry in the developing countries has been widely expressed, most recently in a debate at the United Nations General Assembly in May 1978. The premises on which the protagonists based their arguments are so different that a dispassionate analysis of the problem is obviously necessary.

Innovation

Much has been said about the adverse effects and the misuse of existing medicines. While these are important aspects of the public's interest in the industry, they cannot be treated in isolation from the benefits conferred by modern medicines. Our concern should be to ensure an improvement in the ratio between benefits and unwanted effects. New chemical entities or better delivery systems may enable us to increase the benefits, or, alternatively, to reduce the unwanted effects. Either way, progress depends on the success of pharmaceutical innovation. The dwindling flow of new products, in spite of substantial increases in research expenditure, should therefore provoke deep public concern. Before the trend can be remedied,

its causes must be ascertained and the complexity and nature of innovation comprehended.

The discovery of new medicines involves scientific skill, creativity, time, money and other material resources. During the long-term development of a project the number of people involved, and the costs incurred, tend to rise exponentially. To minimise the costs and to ensure that resources are put where there is the best chance of results, it is not enough to put together the necessary multi-disciplinary team and help them to achieve a group sense of purpose and commitment. Management must also have the discipline and authority to stop less promising projects before large resources are invested in them. One of the main reasons for industry's success in pharmaceutical innovation, in comparison with the relative failure of state or academic pharmaceutical research, may well follow from its need to survive in a fiercely competitive world. The harsh but inescapable facts of commercial life often provide the spur for taking decisions to stop particular projects which, in other circumstances, might have continued to swallow effort and resources for long and unproductive periods.

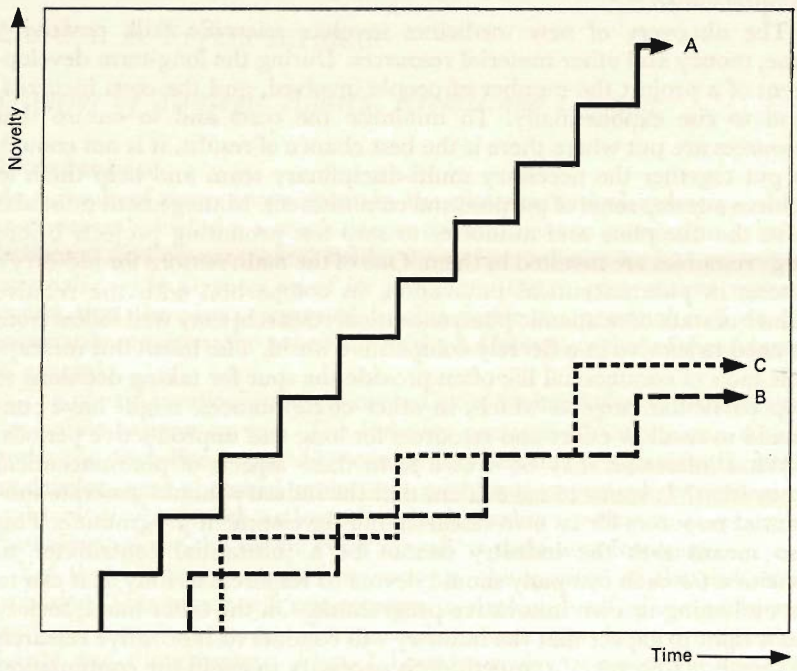
What inferences may be drawn from these aspects of pharmaceutical innovation? It seems to me evident that the industry should generate substantial resources for its own research and development programme. This also means that the industry cannot be a substantial contributor to charities, for each company should devote its resources as fully as it can to strengthening its own innovative programme. On the other hand, society has a right to expect that the industry will conduct its innovative research efficiently. However, if competition is necessary to avoid the continuation of unproductive research, it must also be accepted that competition inevitably leads to some degree of waste through lack of research co-ordination and duplication of effort. If we want the benefits, we must not be too intolerant of some of the disadvantages inherent in a commercial framework.

Nor must we forget the enormous costs incurred in successful pharmaceutical research. World-wide, the industry probably spends more than £1 billion a year exclusively on finding new chemical entities (out of the very nearly £2 billion total appropriation for Research and Development). The result of this vast research programme is a handful of major advances each year. In addition, there are many more minor advances – for example, reformulations which may bring about a longer duration of action or a degree of better absorption of a particular medicine.

Many observers decry these small gains, but no pharmaceutical company I know of can so arrange its affairs as to produce only major advances. Indeed, it is also true of industries other than pharmaceuticals that the most efficient use of resources results from deliberate attempts to make forward steps on a moderate scale. The leap forward has an obvious and natural appeal, both to the scientist and to society as represented by the average man, but important progress more often results from a series of small steps, none of which alone might seem to accomplish much.

I like to think of the process of innovation in terms of a staircase. Both the depth of the treads and the height of the risers are important in determining the time it takes to attain a given objective. In the case of the industry, the eventual height achieved represents the innovative progress

FIGURE 1



A = Theoretical norm.
B = As for 'A' but projects take + 150 per cent time.
C = Projects more original but take + 200 per cent time.

made. As the illustration shows, the theoretical norm is one in which each tread is so much higher than the one below that innovation rises fairly quickly to an impressive eventual height, (A).

If the depths of the treads is increased (B), costs rise with the result that we can afford fewer staircases. If all are similarly affected, projects will be managed more cautiously and the rise for each step will be shallower. Sponsoring more original and more protracted projects with the aim of producing a higher rise does not necessarily help very much (C).

The compounding effect of the different causes of delay on the overall rate of progress can be dramatic.

The number of staircases in simultaneous construction and their average rate of rise determine the overall new product output of the world's industry. That the general slope of the staircases is becoming flatter (more like 'B' than 'A') is worrying enough; when taken together with the decreasing real investment in the innovatory part of R and D, the trend becomes alarming. Yet Cromie's account of the largest pharmaceutical company's (Hoechst) experience and his projection of the trends found show that this company's innovation share of the R and D budget will have halved in less than ten years. There is no reason to think that other companies are faring significantly better.[1]

Factors which prolong projects

Twenty-five years ago, the time from the inception of a project to the stage where its commercial future could be clearly discerned (the depth of the tread of the staircase) rarely exceeded two or three years. Now the period lasts from ten to fifteen years. There are many explanations for this, but I would first like to discuss some of the implications which have not, so far as I know, received adequate attention. With such a long time between the inception of an idea and its practical realisation, companies must have more projects that are active at any one time if they are to achieve the same numerical output.

Obviously, this means that product development has become much more expensive and the extra expense of longer projects is compounded by the interest due as a result of the long lead time between expenditure and achieving the first financial rewards. Also, the efficiency of decision-making in research becomes less the longer projects take to complete. Until a successful step provides a relatively firm basis for the succeeding one the direction of research must proceed in relative darkness. The time per stair factor (if I may return to my staircase analogy) also governs the overall rate of progress by the industry because publication, which stimulates others, will also be delayed.

The management of industrial research is a process of taking repeated subjective decisions on the risk/benefit ratio of the enormous number of alternatives which crop up as possibilities during the course of each project. Accountability for results is the best motivation for getting these decisions right and good managers tend to place their confidence in a research scientist with proven ability. But to be only able to judge the wisdom of a person's research decisions after a span of ten to fifteen years is unreal. Additional problems confront management as well. How will one be able to decide from a large team who are the inventors so that they can be rewarded as the new patent act requires and how can one diminish the additional stresses that this new self-interest factor will put upon the team spirit? How can wise commercial decisions be taken in the light of market expectations so far ahead? Who in 1978 has such prescience that he would be willing to forecast what medicines would be most appropriate to the conditions prevailing in 1990? Yet these are precisely the questions which face the boards of research-based pharmaceutical companies today.

Then there is the inevitable change in staff which takes place over so long a period as ten to fifteen years. So many people are involved in the course of a single project that its direction easily becomes confused and uncertain. The long lead time furthermore increases overall costs because, while everyone waits to see if the first clinical results are in line with laboratory predictions, the team continues its activities, synthesising and testing new compounds while the chosen one is worked up and clinically evaluated. If the assumptions prove to be wrong when the substance is tested in man, then almost all the extra work will tend to be fruitless as well.

The long lead time has naturally prompted management to minimise some of the unfortunate consequences of delay, although some of these part-solutions cause problems of their own. For example, many aspects of the project are now investigated in parallel, despite the disadvantage that

some things will be done which a sequential approach would have shown were unnecessary. The emphasis on saving as much time as possible has other unfortunate effects, too. The obvious example here is the use of established biological models of disease. To work up a new and better model rarely takes less than five years but to add this period on to an existing delay of ten to fifteen years is quite unacceptable. The result is that pharmaceutical research too often relies on existing models, even though these are imperfect predictors of human therapeutic activity.

The disadvantage from society's viewpoint is that the existing selection methods frequently pick out compounds with a similar pattern of action to those already available. More companies are therefore likely to end up with similar products with similar unwanted effects, when diversity is what we should aim to achieve.

Nor should it be imagined that all these constraints on the innovative system in the pharmaceutical industry are unimportant to management, who depend heavily on the success of their innovation. Neither of the two companies with the largest share of the prescription medicine market in the United Kingdom in the late 1950s now ranks as high as twentieth from the top. There are probably several explanations for this decline, but lack of successful innovation must be placed high on the list. In contrast, the most successful companies, whether judged by their market shares, stock market valuation or by their prestige, are those which have made greater numbers of useful small innovatory steps interspersed with a few major advances.

While lack of successful innovation obviously arises from many causes, including perhaps timidity or an unimaginative approach on the part of decision-makers, the chances of commercial success diminish the longer the project takes. From comparison with other industries, it is clear that seven years is about as long as it is prudent to take to complete a single step project. Any longer period compels management to a more cautious, less ambitious approach, which increases the amount of near-duplication and diminishes the significance of many of the steps of innovation. Such an outcome benefits neither the industry nor society.

Regulation and new knowledge

The requirements of regulatory agencies have grown year by year, so that it takes longer to generate the information needed to satisfy them. Furthermore, the delays incurred in assembling the completed mass of data, making a submission and waiting for it to be considered on at least two occasions, as required for registration, probably average at least 15 to 18 months for new chemical entities.

All the signs point to still longer delays in the future, if only because new tests for ensuring safety are always being developed and must inevitably add to the time schedule. So even without the imposition of new controls, costs will continue to rise.

Increasing costs of research cannot be passed on indefinitely without eventually reducing the usage of the product. At some point there must be a cost ceiling above which industrial R and D becomes uneconomic and accordingly will be brought to a halt. Whether this ceiling has yet been reached is arguable, but it is certain that a continuation of the trends I

have described in this paper will, sooner rather than later, take costs beyond any sustainable level.

To my mind, the most important problem facing the industry, the regulatory agencies and that segment of the public concerned that useful new medicines should continue to be developed, is the constraint that time places on innovation. Weeks or even months cut from the total time schedule are quite inadequate. What we must do is to reduce the project period to seven years or less. If we cannot, then both industry and society will have to accept the consequences: reduced numbers of new chemical entities produced at an ever-increasing cost, with fewer of them representing a substantial advance on those already available. It will also mean that little can be done for the less common diseases or for those where there is no established laboratory model.

Equally disheartening is the fact that those remedies that do at last emerge from the lengthy, drawn-out process may well have been over-researched. This produces two ill effects. First, it deprives other projects of resources and, second, it deprives patients of the benefits that the product could have conferred. This type of 'drug lag' has recently begun to provoke major criticism in America. In this country, Sir Derrick Dunlop has pointedly observed: 'It is possible that any increased safety of drugs achieved by the stringent regulations required nowadays is outweighed by the delay and expense of introducing, or even postponing altogether, valuable new remedies.'[2]

Some practical suggestions

What are we to do in the face of these unpleasant realities? Of course, there are many ways in which short periods of time could be saved. All of them should be pursued as their combined effect could well be substantial. But, mindful of the need to save years rather than months, I believe radical changes in our approach are needed as well. Four possibilities are worth discussing:

(i) Sir Derrick Dunlop, with his desire to shorten the development period, has put his finger on one of them: 'A shift of requirements is therefore necessary from further elaboration of preregistration tests to effective systems of monitoring after marketing.'[2] There is an obvious danger here that, instead of being used to reduce preregistration requirements, monitoring will simply be superimposed on them.

(ii) Delay could be reduced if some voluntary patients (healthy volunteers already play a valuable role) were able to receive therapeutic doses of a new substance under close supervision at a much earlier stage than is now permitted in the United Kingdom. For this purpose, a special group of 'patient volunteers' would be needed. Adequate safeguards would obviously be essential, including notification to the registration authorities. The responsibility for the decision should nevertheless rest on the clinicians, the ethical committees of the hospitals, the pharmaceutical company and, above all, the volunteer, who should be able to give informed consent.

(iii) Any alternative registration procedure which minimises the delays from assembly and review should be examined. One I have in mind might be more appropriate for some new products than the present uniform system. It proposes that a company should be able to opt for a scheme in

which a member of the licensing authority and one of its advisors from the CSM play key roles. Together with other experts they would sit on a regulatory project group, which would meet regularly on the company's premises. Here it would have access to data on related compounds as well as the product candidate, hold discussions with company scientists and monitor at close hand the work in progress. Ultimately, the stage should be reached when the project group agrees with the company that only a few remaining studies need to be satisfactorily completed before marketing. At this stage, ie, while the remaining studies were being conducted, the company could formally submit their findings to date, together with the protocols for the remaining studies, to the licensing authority. The authority would be asked to review the work done and agree that the project group could have delegated authority to complete the CSM's consideration of the product, provided the results of the remaining studies were satisfactory. On receipt of a notice from the project group to this effect the authority should be able to issue a licence speedily. A similar procedure could be evolved, either to deal with applications for a clinical trial certificate for certain drugs, or for limited marketing with surveillance.

(iv) I would also welcome re-examination of the idea of a research institute, sponsored by industry and government, to undertake primarily the sort of preliminary work that could shorten the initiation period of company projects. The successful establishment of new disease models, and understanding of mechanisms of disease, by the institute would take the time needed for such studies off the opening period of company projects. If every year there were a few new models of disease, companies would use the knowledge eagerly. The result would also be a diversification of the whole industry's approach to research with increased public benefit. Why not, you may think, suggest that this kind of work be undertaken in universities? I would argue that the development of a new test system requires major multi-disciplinary efforts in the applied sciences. Universities are unlikely to be effective organisers of such projects. Nor would individual companies necessarily be the most effective. It seems to me that a separate research institute is likely to provide a more economic as well as a more practical solution to this and a substantial number of other problems, including probably more accurate and faster predictors of human toxicology, assay methods for metabolites, enzymes, hormones, etc. Companies who supported the institute would be permitted access to work in progress and prior to publication. They would get help in establishing any new model/test system in their own laboratories and perhaps even arrange for the institute to do some tests on their compounds.

No doubt there are other ideas which should be explored if the pharmaceutical industry is to regain some of the innovative enterprise and daring which led to the pharmaceutical revolution of the 1940s and 1950s. But a prerequisite to any new stimulus must be a better understanding of the industry and its problems, coupled with a willingness to modify the constraints imposed on it by the economic and social climate in which it now operates.

Developing countries

The second theme I propose to explore is the relationship between the

industry and countries in the Third World. Many people have looked at the prices of medicines, noted the large margin between direct costs and the sale price of medicines and too easily concluded that something was radically wrong. Developing countries in particular, it appeared, were being exploited by the multi-national research-based segment of the industry. Some countries were prompted by this belief to adopt a markedly negative attitude to this type of pharmaceutical company.

I do not wish to suggest that the industry is anywhere near perfect. No doubt it has many irritating and wasteful characteristics. But I believe it is important to emphasise that any form of complex human activity tends to be less efficient than one would wish, whether carried out by an individual pharmaceutical company or by a government organisation. To believe that government intervention necessarily solves economic problems is to take refuge in an illusion.

Compare, for example, the consequences of the very different economic and pharmaceutical policies adopted by Sri Lanka and Singapore and, as far as we are able to do so, the consequences that followed. The two islands differ substantially in many ways that limit their strict comparability: for instance Singapore has a much smaller population and fewer natural resources. Sri Lanka adopted a generally negative policy to the research-based pharmaceutical industry in particular, and multi-national companies in general. This culminated between 1972 and 1977 in a State Pharmaceuticals Corporation which was responsible for procuring all drugs. Singapore, on the other hand, followed a positive line of co-operation with multi-national companies in many industries.

Both initially had low incomes per head of population, but the latest figures show that a wide gap has developed between the GNP per head for the two countries (Table 1). Singapore continues to have rapid growth and a strong currency. As the Table shows, this is reflected in the high expenditure on health per head of population, whereas that of Sri Lanka is twenty times less. In a review of Singapore's progress Cicely Williams wrote: 'The vast improvement in health is not due to specialisation nor mass campaigns for disease control or birth control, but is due to gradual

TABLE 1

Country	*Population (millions)*	*Infant mortality per thousand*	*Percentage enrolment in primary school*	*Health expenditure (US $ per capita)*	*GNP (US $ per capita)*	*Percentage of population under 20*
Australia	13·9	16	100	131·9	5,640	28
Singapore	2·3	14	60	62·0	2,648	46
Sri Lanka	14·1	45	89	2·97	150	89

From: 'Far Eastern Economic Review'.[4]
Figures taken are latest available in each separate country.

establishment of law and order, health and education and economic development. The remarkable reduction in birth rate from 50 per 1,000 in 1950 to about 12 per 1,000 now is due to the child care, not to vast expenditure on birth control.'[3] This conclusion is supported by the figures in Table 1 which show the infant mortality rate to be three times lower in Singapore than Sri Lanka.

Now of course I do not wish to suggest that Singapore has done so well simply because she adopted a positive policy towards co-operation with multi-national companies in the pharmaceutical and other industries. Many other aspects of economic and social policy undoubtedly played a vital role. Nor do I suggest that the GNP per head of population provides the only or even the best measure of outcome. Whatever evidence there is nonetheless indicates that there are profound differences in the consequences of a positive policy, which accepts the need for technological progress on the one hand and a closed (or half-closed) door to it on the other. Pharmaceuticals are swept along in whatever policy is adopted.

And it is surely significant that Sri Lanka appears now to be substantially reversing its original negative approach. Dr Fernando, the Sri Lankan Deputy Director of Medical Services, indeed cited a number of interesting major reasons for the failure of the original pharmaceutical policy.[5] His government experienced difficult problems in trying to buy the cheapest products available. Quality could not always be ensured; unpredictability in the action of certain medicines confused the practice of good medicine, with potential danger to health or life; medical frustration and a high rate (40 per cent) of medical emigration added to the problems.

None of this is to say that a community like Burma, which has opted out of any participation in technological innovation, is wrong to do so. Social and other factors often determine the lines a particular government feels compelled to follow. What can be said is that those communities who seek more wealth and who do not have valuable minerals to barter for it had best embrace technology. To do so does not necessarily mean that the community must sacrifice its cherished traditions or cultural values.

This is not the place for a full review of the economic effect of multinational pharmaceutical companies in developing countries. But two or three illustrations seem appropriate. Studies in Brazil and Argentina concluded that multi-nationals contributed 43.3 per cent and more than 30 per cent respectively to their export of manufactured goods.[6] The concomitant change in the distribution of wealth has been analysed by Fields.[7] He observed that: '. . . the poor in Brazil clearly *did* share in a decade of economic development. Some poor were lifted out of poverty. For those left behind, their income grew at least as rapidly as those of the non-poor . . . Relative inequality did become greater by most measures.'

A pharmaceutical industry study for India estimated[8] that in 1975–76 the 'foreign' (ie, more than 40 per cent foreign equity participation) pharmaceutical sector contributed US$53.4 million net of foreign exchange, mainly by import substitution but including substantial exports.

The figures are small for such a large country. On the other hand, it must be noted that the industrial economy of India is still small and that its policy has been one of varying levels of discouragement of multi-

TABLE 2 **India foreign exchange contribution of multi-national companies. Inflow – Outflow 1975–76 (US$ Millions)***

	Inflow *Exports*	*Outflow* *Remittances*
1973–74	9·5	5·2
1974–75	13·3	2·3

	Import Substitution		*Imports*	
1975–76	64·3	13·6	19·8	4·7
	77·9		24·5	

Therefore net gain inflow/outflow=US$53.4 million.
*US$=Rs 8.09.
(Remittances in 1975–76 amounted to 35 per cent of export sales and have been taken into the above figures.)

national companies, even if this has stopped short of prohibition or nationalisation.

It strikes me as a pity that we do not yet have a series of case studies on developing countries to show the effect on the balance of payments and on the country's health of policies with various levels of co-operation with multi-national companies. Important studies of this kind are now in progress. However, I believe that sufficient evidence exists to permit a more detailed analysis than I have attempted here. And I suspect that, when such an analysis becomes available, many more countries will decide that a positive policy serves the national interest better than a closed (or half-closed) door.

A positive policy aims to make full use of existing technology as well as new developments. Various aspects need to be discussed:

1 *General economic factors*

The policy must be based on increasing wealth through industrialisation to the maximum extent practicable with the aim that this will generate the funds needed for further growth and other purposes. To do this efficiently, capital has to be husbanded and put to use where it will generate the greatest surplus so that further investment is enhanced. This means especially where there is a very low level of capital invested per worker, that the resources must be directed to the small minority of the population already using modestly sophisticated services, factories and equipment to produce standard goods. To minimise commercial risks, these goods should be those whose effectiveness and satisfactory nature have been established by wide usage throughout the world for several years. If they were the subject of patents these will have expired and the patent will have disclosed some of the essential know-how.

The development of the economy requires that the amount of capital per worker, and the number of workers in the industrial sector, increase substantially each year.

In these circumstances, multi-national companies can play an important role:

(i) If local conditions are encouraging they will 'transfer in' valuable technology.
(ii) They will provide employment and the training to help local staff to reach high standards.
(iii) Local production will reduce the need for imports.
(iv) Most of the capital for the local operation will come from the multinational company's own resources.
(v) In time, they can be persuaded to generate exports.
(vi) They may help to exploit and process locally indigenous raw materials, thereby increasing the value-added locally.
Once a large enough number of people are absorbed into the industrial sector; education, industrial experience and ambition inevitably create a situation where some of them wish, and have the ability, to become innovators themselves. To obtain financial advantage from their potential creative drive, the country will need to subscribe to international patent and proprietary rights conventions in order to use exploitation through licensees as a way of overcoming local financial, marketing and manufacturing weaknesses.

2 *Medical services*
Developing countries are generally better advised to concentrate their medical services initially on improving hygiene and by devoting resources to health education, nutrition and family planning.

At this stage, they may have to tolerate a situation where the classic pattern of western medicine, with its emphasis on diagnostic and curative facilities for the individual, is mainly available to a minority – usually in the urban and industrial sectors of the community.

There is, however, a useful role to be played by the commonly available 'home medicines', which can be used for the symptomatic treatment of self-limiting conditions. Home medicines of this kind cost very little, produce a considerable benefit and come within the reach of ordinary people even in poorer regions of developing countries.

With severely limited medical resources some diseases can probably be dealt with in less developed countries only by 'packaged programmes' for individual diseases, made up of diagnostic procedures and treatment systems, suitable for operation by trained and supervised technicians. Such systems might be developed (and approved by the authorities) to control a number of endemic diseases.*

3 *The role of industry*
The costs of communication in developing countries are substantial. Even so, dissemination of information, education and promotion of certain products and measures are essential if the standards of nutrition and home-care are to rise. A guiding principle must be that emphasis is placed on practical solutions rather than on just communicating abstract con-

*Eg, amoebiasis, where it seems possible that the simplification of a precipitin test to the level already achieved by Ames with a latex agglutination test, could provide a reliable diagnostic duo.[9] Suitable treatments already exist for amoebiasis.

cepts. Communication is more effective, for example, if it deals with a certain product or a particular article of diet.

As indicated above, home medicines have a useful role to play. They are already widely used in some of the poorer countries. The industry provides them at low overall cost and, in the process, establishes cost-effective communication channels and trains a number of workers in aspects of health and hygiene, nutrition and self-care. It is reasonable to believe that the pharmaceutical industry might also undertake the management and supervision of some of the 'packaged programmes' referred to above, since it possesses the skills to develop diagnostic methods suitable for field use and to train and supervise local technicians in their use. If the financial motivation existed, the industry would willingly undertake the management, distribution and supervision of such a 'packaged programme'. Indeed, the successful distribution of condoms by a multinational company into even the smallest villages of Sri Lanka, on behalf of a major family planning programme, lends credibility to this concept.

The developing countries are also likely to derive great benefit, at a relatively low cost, from products which are already out of patent protection. Most of the items on the WHO 'Essential Drug List' of 1977 are either out of patent or will be by 1979. Only four have patents that do not expire by 1980. Parenthetically, it is worth noting that the 'Essential Drug List' is composed largely of chemical substances that did not exist before 1945 and would probably not have existed without the spur given to pharmaceutical research by patent protection.

Evolution of pharmaceutical supply policy

Stage 1

In regard to the curative, ie, medically controlled aspects of health care, the role of the industry in developing countries will not differ significantly from that in developed countries, although generic drugs will play a more substantial role. The cheapest products that reach an adequate specification will no doubt be chosen, always provided that quality can be ensured. The Sri Lankan experience shows how important it is that medicines should be bought from reputable sources and that contract analyses be used as a further check. Most countries will import their generic products; a few of the larger and more developed nations will doubtless start manufacturing and testing generic products themselves.

Suitable 'packaged programmes' should be welcomed and their development should be encouraged by countries with the same needs. Home medication by symptomatic agents should be allowed to spread throughout the country. As to new medicines still under patent protection, some countries will feel compelled to restrict their availability, mainly on grounds of cost but also because they can only be used effectively under proper medical supervision, and that itself is limited. The hope must be that rapid progress in economic growth will increase the number of doctors and the general availability of all important medicines throughout the world.

Stage 2

Some of the smallest and least-developed countries are unlikely to devote

much effort to pharmaceutical manufacture, for they have little to gain from it. Limited manufacture nevertheless becomes feasible and sensible at quite modest stages of industrial development. At all levels, there is a need for supply, marketing and technical services for a range of products.

When a country begins pharmaceutical manufacture it will almost certainly concentrate on finished generic products. The innovating multinational companies do not usually possess any unique ability to manufacture many generics, but expert knowledge can be obtained from a large number of manufacturers who specialise in this field. Certainly, this would be more economic than trying ro 're-invent' a pharmaceutical process in each developing country.

Third World based multi-nationals might at a later stage play an important role in generic manufacture, as Lall has suggested in an article in the *Guardian*.[10]

Stage 3

A country with a substantial population may well reach a stage when local manufacture of at least some ingredients becomes desirable, although the availability of foreign exchange tends to limit the rate at which more sophisticated technology can be introduced. On the other hand, substituting local manufacture for imports makes a useful contribution to the balance of payments, as was noted above in the discussion on the Indian situation. Multi-national companies become more important at this stage, if only because they usually provide their own capital and know-how.

Stage 4

A number of developing countries will eventually aim at fuller chemical manufacture, later progressing to more sophisticated levels of pharmaceutical technology. It is at this point that the patent system will prove of particularly great value in making available technical details and know-how. Developing countries should therefore adopt a positive attitude to the world-wide patent system. If the present system could in fact be developed and extended so that more of the know-how, which is not at present patentable and tends to be kept secret, came into the open, then the Third World would in time be a major beneficiary. Unfortunately, some of the developing countries fail to discern that publication is the fee exacted by society for the benefits to the patentee from protection by the patent system, and that publication gives them and other countries access to information which would otherwise be denied them.

At present, some of the more advanced developing countries do not subscribe to the international patent convention. The advantage so gained tends to be short-term. Not only does it limit the amount of information research-based multi-national companies are willing to publish, but it places constraints on the development of their own technology.

The importance of high-level pharmaceutical technology in a developing country should not be minimised, for together with other technological innovations, it can generate wealth on a broad front. The benefits to Singapore of a positive approach to technology have been referred to

before. A recent case study emphasises the point: pharmaceutical investment in Singapore has led to exports to many other countries, including Japan.[11] If the local conditions for exploiting technology are good enough, then foreign investment is likely to contribute substantially to further development.

Total reliance on foreign investment is of course unwise. To arrive successfully at Stage 4, a developing country needs to stimulate local investment by its own citizens. This requires the type of economic and social climate which ensures that those who have built up their own expertise and resources willingly put them to work in their own country. If, for example, the best medical care available locally is well below the best standards, this tends to drive the most successful innovators abroad and reduces the time, effort and money that they invest in the country. Similarly, a harsh social and economic climate discourages good doctors from working in the country.

Holding back the development of medical services in the industrial sector of a developing country in order to direct resources to rural areas, however sensible it may seem in the short term, carries a long-term hazard in that it may impede economic development. The result could well be a poorer rural medical service than might otherwise have been the case.

International Investment

To meet the special needs of developing countries R and D investment is necessary. However it is funded it is likely to be most productive if it is committed where the existing record shows a high level of success. New chemical entities or new diagnostic tests are needed to deal with some of the endemic diseases found commonly in the Third World. Nor is the discovery of these new medicines and tests enough. Once discovered, they should be assembled in complete 'packaged programmes' which could be used by specially trained technicians without the need to involve Western-type hospital investigation and treatment.

We need to determine from the research-based pharmaceutical companies what sort of incentive would make this research attractive. The companies might be willing to put forward a series of proposals, which would probably include some financial arrangement with bodies like the WHO, on the basis of which they would undertake the work. The companies might also ask for special patent protection so that any invention will be given a long enough time for the innovator to feel that his original investment – in time, resources and priorities, as well as money – could be justified.

Another field which requires exploration concerns the factors which determine a multi-national company's attitude to participating in the economies of developing countries. The steps in the process are well-established. It begins with marketing of some products; if this proves successful, local manufacture begins; later, continued success and the growth of confidence could lead to the consideration of a local R and D facility. What prompts a company to invest money in a developing country is less well-established.

To try and define some of these factors more precisely, the OHE has conducted a survey among 65 major companies. Of the 15 factors listed

TABLE 3

Factors Affecting Decision to:	(A) Enter market (B) Establish factory (C) Establish R and D laboratory		
	'A'	*'B'*	*'C'*
Confidence in future of the market	122	117	110
Pressures for generic prescribing and attack on brand names	115	71	76
Threats of a 'restricted prescribing list' or similar controls	114	73	84
Controls on volume and methods of promotion	114	44	36
Strictness of price control	110	79	48
Control on content of promotion	100	22	32
Effectiveness of patent protection	94	78	110
Current level of company profits	78	94	99
Wage and salary levels	59	95	76
Tax 'honeymoons' and similar inducements	52	104	86
Insistence on national rather than overseas staff	42	58	77
Capital grants or loans on favourable terms	33	116	84
Availability of scientists	27	85	121
Availability of technologists/technicians	25	99	110

28 respondents scoring from 1 to a maximum of 5.

in Table 3, most appeared to be important as judged by the replies received (from 28 companies). Those where the average score exceeded 110 should be interpreted as meaning that a poor climate for one of these factors would make entry into the market very unlikely. A score of 105 or less for one or two factors must still be regarded as unfavourable, but a positive decision might nevertheless be made if the other factors justified it.

Several aspects of the replies need particular emphasis:

(i) As expected, relevant financial factors are all very important. Marketing involves relatively little capital, so factors affecting the cost of capital are not very important, whereas they rate highly in the establishment of a factory.

(ii) The 'people factors' show generally the lowest numerical ratings. This suggests that pharmaceutical companies readily accept the need to train local people and pay good salaries.

(iii) Only for R and D investment does patent protection become critical. The obvious implication is that marketing and manufacturing companies expect generic competition from older products.

(iv) Freedom of method and volume of promotion appears more important than freedom of content, probably because companies accept the need for factual claims and are not therefore unduly concerned about the control of promotional content. However, official pressure on doctors to use competing generic medicines is seen as an unacceptable distortion of the market-place. Even higher scores might have been given had respondents thought that governments would succeed in forcing doctors to use products from an official list.

(v) The answers appear to give less weight to the factors that might in

practice prove the most volatile. If the survey had asked about long-term controls on company profits, then presumably the scores for this factor would have risen to match that for price control.

Developing countries have many health needs which are pressing and which cannot be provided by the research-based multi-nationals so a policy towards them can only be a part, albeit an important part, of the host country's health strategy. A policy on pharmaceuticals is also part of an industrial strategy and for those countries that wish to industrialise there are good reasons why a policy of using technology very positively should be adopted and should embrace the pharmaceutical component of industry.

REFERENCES

1 Cromie B W. Innovation in the Pharmaceutical Industry. *British Medical Journal*, 1978, vol 1, pp 1618–19, and Medicines for the Year 2000. OHE Symposium, September 1978.
2 Dunlop Sir Derrick. The state of British medicine – 5: The innovation, benefits, drawbacks and control of drugs. *Journal Royal Society of Medicine*, vol 71, May 1978, pp 324–30.
3 Williams Cicely D. Family Health Services and Vital Statistics: lessons from Singapore. *British Medical Journal*, 1978, vol 2, pp 51–52.
4 *Far Eastern Economic Review*. 25 November 1977, p 34.
5 Fernando S D. Sri Lankan Presentation at WHO General Assembly, Geneva, May 1978.
6 Nayyar Deepak. Transnational Corporations and Exports. *The Economic Journal*, vol 88, No 349, March 1978, pp 59–84.
7 Fields Gary S. Who Benefits from Economic Development? – A Re-examination of Brazilian Growth in the 1960s. *The American Economic Review*, September 1977, vol 67, No 4, pp 570–82.
8 OPPi 1978.
9 Editorial. *British Medical Journal*, 1978, vol 2, pp 379–80.
10 Lall Sanjaya. The new multinationals. *Guardian*, 12 June 1978.
11 Smith Charles. Exporting to Japan – Local Springboard for Beecham. *Financial Times*, 30 December 1977.

Discussants

Dr M. L. BURSTALL *(University of Surrey, Britain)*

During the past forty years the pharmaceutical industry has developed through competitive innovation. Can this continue, and, if so, how? These are the questions which underlie much of what has been said this morning and, indeed, yesterday.

In outline the problem is simple. The cost of innovation has risen dramatically in recent years, due partly to more stringent safety regulations and partly to the depletion of research opportunities. At the same time profit margins are under pressure and the return on innovatory research has fallen to levels which are distinctly unattractive when the risks involved are considered. If innovation is to continue, where are the necessary funds to come from? There can be only one answer: from those who benefit, whether payment is by the consumer or, as is more usually the case, the government agency.

At the national level pricing policies involve a conflict of interests. Cost-effective medical care requires that drugs be as cheap as possible; at the same time the development of new products must be financed by the sales of existing ones. It may be that this would not matter if all countries were involved in product innovation. As we all know, however, this is confined to a limited number of advanced nations among which Germany, Switzerland, the USA and the UK are pre-eminent. The world is divided into those who innovate and those who do not. It is not surprising that this situation is often a cause of ill-will. The non-innovative countries feel that they are in effect taxed to aid the development of products in which they have a limited interest; with equal justice the innovators complain that others use their skills and do not pay for them.

Will the capacity to innovate become more widely diffused? As far as product innovation is concerned, this seems unlikely. The OHE survey confirms what earlier studies, including my own, have suggested. Multinational pharmaceutical companies place major research establishments in countries which are politically stable, have favourable economic policies, a large and flourishing scientific community and a proven track record of success in innovation. Few developing countries meet these criteria. Nor is it likely that they will readily develop an indigenous capacity for product innovation; the necessary infrastructure is not there.

The outlook for other types of innovation is much brighter. The skills required for process innovation can to a considerable extent be transferred from other parts of the fine chemical industry, while the development of existing products to suit local markets is usually the first type of R and D to be introduced by foreign multinationals to host countries. A large developing nation with a substantial stock of cheap skilled manpower could well develop a considerable pharmaceutical industry on a medium-technology basis. I would not be surprised if one or two Indian multinationals of this type emerged within a decade or so; it will be interesting to see how they are received in the smaller developing countries.

If this version of the future comes about, then Dr Lall's suggestions for

improving relations between the innovating and the non-innovating countries have much to commend them. Each has the power to hurt the other; neither will benefit by doing so. One might go further. Would not the multinational companies be wise to concentrate on product innovation and the provision of skills and to subcontract production and marketing to indigenous companies? This might well be the most acceptable course of action in political terms.

So far I have, of course, assumed a surprise-free future, in which existing trends continue and the trees grow up to the sky. This may not happen. It is possible, for example, to envisage developments which could reduce, perhaps drastically, the costs of innovation. The attitudes of governments could change as they become more familiar with the complexities of the situation. In this connection it would be interesting to know whether the industry is, in political terms, dealing with *a* public or *the* public. If, as I suspect, the former, the creation of a favourable climate of opinion may be easier than most people now think.

We must also remember that cell biology, biochemistry and molecular biology have been the great growth areas of pure science since the Second World War. It would be surprising if this work did not yield insights into the causes and possible cures of the major killers of today. There are other possibilities. As a former chemist I am much impressed with the potential of quantum pharmacology and of the computer-assisted selection of synthetic routes. Developments of this type would reduce very considerably the need for many kinds of skilled manpower. Having spent several years of my youth trying to synthesise tetracycline I might deplore such deskilling techniques; as a friend of the industry and a firm believer in the law of least effort I welcome their advent.

The effects of such changes are likely to be quite complex. It can be said with some confidence that they would reduce the price of a ticket to the game. Some kinds of manpower would become less valuable while others, perhaps more mathematical and theoretical, would become more so. Further than that it is difficult to say. We shall just have to wait and see what happens.

PROFESSOR E. KAUFER *(Innsbruck University, Austria)*

Lord Vaizey, ladies and gentlemen, all three papers are stimulating, because agreement is near where disagreement seems to be present. When I read Dr Lall's paper for the first time I felt a sense of despair not because he has uncovered so many unsolved problems but because he appears to be pessimistic about their solubility. On various occasions he points to defects in the competitive functioning of drug markets and then proposes not the improvement of workable competition but more intervention in what is already an overregulated industry. However, even such a relatively simple task as an essential drug list is demanding in terms of the ability and integrity of the administrators. History has taught us that most, or I should perhaps dare say all, regulatory or interventionist bodies are finally captured by some group of society and then run in their own self-interest. I sense that Dr Lall shares some of this scepticism.

Compared to the task of designing the best regulatory institution the improvement of the workability of competition is (a) analytically quite simple and (b) restores a selfpolicing system where you can let the results take care of themselves. I wish to discuss briefly three points as partial evidence; others could be added.

First, Dr Reekie has demonstrated that there is already an intensity of price-by-product competition that should surprise at least the adherents to the conventional wisdom. In his pioneering study he has shown us that the drug market would respond if subjected to the proper competitive incentives. However, in most industrialised countries, the tax treatment of health insurance induces people to overinsure. But overinsurance lowers the price elasticity and increases the quality elasticity of demand also for drugs. Eliminate overinsurance and the doctor has the incentive to select the treatment that is most cost-efficient for each patient individually.

Second, in many countries no price competition at the retail level exists. In my home country, Austria, pharmacies are licensed like liquor shops in a prohibition country.

Third, the regulatory approach to drug safety with its emphasis on ex ante simulation instead of monitored release and post-marketing surveillance puts a heavy burden on both the developed and the less-developed countries. Dr Fryers has shown the devastating impact on the efficiency of the internal R and D process. But the long lead-time and the high costs of drug development force the innovating companies to try to lengthen the effective protection of their products by refusing licences in order to establish an exclusive trademark position. This hurts the less-developed countries (LDCs) and the small companies which some 10 to 15 years ago were quite able to secure valuable licences. This is but another aspect of the concentration increasing impact of safety regulation.

Finally, the international control of drug markets is a jungle of protectionist devices and beggar-my-neighbour policies. This is even the case where we ought to have a common market: in the EEC. I believe it is impossible to devise a rational incentive structure linking LDCs and MNCs if these controls persist. However, I foresee that some developed countries will be forced to rationalise the insurance system by abolishing the preferential tax treatment, to lessen the restraints of competition at the retail level, and to – hopefully – take a less wasteful approach to drug safety. More competition in the developed countries along these lines will automatically solve some of the pressing problems also of the LDCs.

DR J. PARKER *(Otago University, New Zealand)*

I shall confine my comments to Dr Duncan Reekie's paper on Economic Competition in Pharmaceuticals. What this paper does for me is to illustrate and confirm how complex the nature of rivalry is in pharmaceuticals. I want to emphasise the special nature of competition in this industry and then reinterpret what I think his results show in a deliberately controversial way, to draw attention to the problem of innovation in the year 2000. Rivalry has three major elements in this industry. First entry: this can be entry from outside, from completely new firms, and entry by

firms in the industry but not in the same sub-market. Entry has the effect of putting pressure on existing companies.

The second dimension is a time dimension, where the 'product life cycle' is in action, whereby the products mature first, by the process of time and by people becoming more skilled at producing these products, and second, by the process of innovation by the companies themselves and other companies. That process has a number of names in economics, and I can remember at least five. It is called product competition, substitute competition, innovative competition, technological competition and dynamic competition and there might be a sixth, workable competition. All of these draw attention to the non-conventional type of competition, where the emphasis is on changing the nature of the product rather than selling a standard product at the same price or lower. The third element in rivalry is the normal one, namely, price rivalry for a product which is relatively standardised. In rarified models of competition, this is the only real form of competition.

What we are saying is that in this industry the conventional expectation is that because we have a credence good, sold via third party purchasers, it will be unresponsive to price elements.

Dr Duncan Reekie's paper suggests that price elements, price profiles, and price impacts can be important and, if that is the case, this suggests that price regulation schemes by governments may well be superfluous.

What I want to do now is to reinterpret the findings of the paper in a deliberately controversial way. My interpretation of the findings of the paper are as follows: I think the signs of rising price sensitivity that Dr Duncan Reekie finds suggests that in industries where price elasticity has become relatively high, there is in fact declining innovation, because a mechanism is in operation which is such that where innovation declines customers are tempted by being offered a given product at a cheaper price. If that is the case, then we come up against Dr Wardell's dilemma, which he presented in condensed form, like this: his choice was yesterday's drugs at a lower price or tomorrow's drugs sooner. My reinterpretation of the findings of the paper is that if we have price competition breaking out, then the emphasis is on yesterday's drugs cheaper. My preference is for tomorrow's drugs sooner, so I would not wish to see price competition breaking out so vigorously.

My concern is that I do not think it is necessarily a good thing to exhibit high price elasticity in drug sub-markets for pharmaceuticals. My preference would be to see premium prices at relatively low elasticities, reflecting big steps forward within a particular sub-market.

GENERAL DISCUSSION – SESSION III

Innovation and the means to ensure continued advance formed an important theme of the discussion during the third session of the symposium. Several speakers stressed the need for the development of new drugs and medicines for both the wellbeing of society and the future health of the industry. But widespread concern was apparent at the continued escalation

in research costs and the obstacle this poses for further advance. Throughout the world a diminishing number of companies are still capable of undertaking innovative projects on a significant scale. Mr F. J. Blee (SmithKline Corporation, USA) suggested that this situation could be exacerbated if other countries followed the United States' lead with its proposed Drug Regulation Reform Act which threatens to discourage further entry into the investigative phases of drug and medicine development.

Mr A. J. Merifield (Department of Health and Social Security, Britain) reassured delegates that the desirability of encouraging innovation in pharmaceuticals is officially recognised in Britain. He pointed out that this is implicit in the Pharmaceutical Price Regulation Scheme which attempts to reward technical advance with a rate of return at least comparable with that obtaining in other risk contract areas. Professor J. Mathieu (Roussel Uclaf, France), in agreement with one of Dr M. Burstall's discussion themes, suggested that improvements in basic research technology could be an important factor in the development of new medicines in the future.

The necessity of rapid innovation was, however, questioned by Professor A. L. Cochrane. His argument was based, firstly, on personal experience in a prisoner-of-war camp where he succeeded in treating a large number of fellow prisoners with only a very limited supply of drugs. Secondly, Cochrane suggested that there is insufficient evidence as yet that all new medicines represent substantial advances over existing therapies. In this respect he considered that more comparative clinical trials are needed rather than an unchecked extension of newly available preparations.

A discussion of the nature of rivalry within the pharmaceutical industry stemmed from Dr J. Parker's tripartite division of competition into entry, time and price elements. Dr D. Reekie preferred to bracket the first two together and identify them as roots of effective competition. He disagreed with Parker's apparent suggestion that conventional rarified price competition was a major facet of rivalry in its own right. He claimed that in reality the concept simply does not exist in isolation even though it fills many pages of economics textbooks. Price should therefore be seen as just one of many variables which companies can use to affect their competitive status within the industry.

The much debated issue of the use and availability of the pharmaceutical industry's products in the less developed countries (LDCs) of the world was raised by a number of speakers. In particular, discussion focussed on the so-called 'essential drug' lists. Mr S. M. Peretz (Deputy Executive Vice-President, IFPMA, Switzerland) expressed the view that the concept was a misnomer: the corollary being that all drugs not included in any such catalogue must automatically be regarded as non-essential. Sir Eric Scowen (Committee on Safety of Medicines, Britain), in agreement, raised the question: essential for what or for whom?

In addition to challenging the terminology Scowen suggested that the value of medicines is dependent on the level of expertise with which they can be employed. The inclusion of anti-cancer drugs and insulin in a restricted list, for example, could generate more hazards than benefits in inexperienced hands.

Peretz also drew attention to the fact that restricting the number of drugs available could mean that some individuals are denied therapy when sick. He referred to estimates suggesting that approximately 20 per cent of a population may be expected to be allergic to a specific drug or develop other problems as a result of its use. Consequently, limiting the availability of alternatives could affect the health of up to one-fifth of a given community.

With regard to the question of the responsibility for drawing up an essential drug list, Scowen considered that the most approporiate individuals would be those actually working in the centres of excellence of the developing countries concerned. Cochrane concurred with this view but emphasised that the key to initial success in the efforts to reduce mortality rates in the less developed countries lay in substantial improvements in sanitation and hygiene rather than simply in the availability of modern medicines.

Turning to the problem of the most appropriate means for LDCs to obtain their medicines, Peretz highlighted the conflict between the desire for self-sufficiency in production on the one hand and that for low drug prices on the other. He considered that although industrialisation strategies are in many ways desirable objectives for LDCs it is unlikely that the local establishment of pharmaceutical industries (because of problems of technology and economies of scale) could result in the manufacture of medicines at prices competitive with those obtaining in the world markets.

Bringing the morning's session to a close, Professor W. Wardell suggested an alternative kind of essential list. He proposed a catalogue of those drugs which society would like to possess in order to treat the many conditions (eg, muscular dystrophy, cancer and schizophrenia) for which inadequate therapy exists at the moment. Unmet demands in these and other disease areas indicate forcibly the need for innovation which in turn requires a healthy pharmaceutical industry.

SESSION IV

Prospects for the Future

Chairman *Professor L. Lasagna*

Professor C. Northcote Parkinson, in discussing the finite life spans of all civilisations, has estimated that by the period AD 2000–2200 our own civilisation should be a thing of the past. Such a prognosis at the very least raises some questions about the appropriateness of this last session. To my knowledge, Parkinson is not particularly a student of drug development, but there is a chillingly familiar ring to his list of the signs of cultural decay: excessive taxation; an increasingly numerous, costly and oppressive bureaucracy; inflation; decreased economic growth and investment; over-centralisation, socialism and state monopoly.

Most significant of all, he stresses, is a loss of confidence and a reluctance to plan for the future. I don't know whether anyone would lay the cornerstone for a new cathedral in 1978, but I am reasonably sure that we shall not see the founding of a new, innovative, research-intensive pharmaceutical firm.

Like Brian Cromie and Max Tiefenbacher yesterday, I suspect that our future is more likely to suit Cassandra than Pollyanna. In many quarters within the drug industry I detect cynicism, decreased adventuresomeness, diminishing confidence in long-term R and D efforts and a tendency to emphasise short-term and non-pharmaceutical diversification programmes. All of these trends are exactly wrong for both the public's needs and the health of an innovative drug industry, which should either play the game with a long-range point of view, or not play it at all. (In this respect, the pharmaceutical industry resembles the natural gas and petroleum industries, where there is also a need for substantial capital investment and a considerable lag between the start of research and the finishing of a successful 'product'.)

This is not to say that the drug industry would not exist in *some* form with the new set of attitudes I have stressed. I would, for example, write a scenario in which the drug industry behaves like a public utility, with a minimum of capital investment, R and D or risk, and a guaranteed 'fair' rate of return. Whether this is *desirable* is another matter.

It is important, I submit, to appreciate that the world of drug development is only a microcosmic reflection of the macrocosmic situation obtaining in our whole civilisation. If one speaks to representatives of other industries, one finds the same complaints of over-regulation that one hears from the drug industry. The public, either willingly, actively, or by default through a failure to rein in their governments, will not only in the United States, but in country after country, spend more and more money to support a larger and larger regulatory apparatus which is supposed to protect the public but which in fact will fail to do this in the larger sense, if one means by 'protect the public' to promote the general welfare.

I submit that the public must first of all appreciate that regulations can

become a cancer whose growth is no longer controllable, at which point the body politic can succumb.

The public must realise that we have *not* run out of ideas, and that scientific research is so excitingly productive that our problem is how to keep track of new information and assimilate it.

The public must be reminded that we desperately need better drugs.

The public needs to learn that drugs cause good *and* harm, and that the more sophisticated our cost-benefit calculus can be, the better are the chances for wise decisions. This will require us to quantify therapeutic outcome with more care than we have in the past.

The public must beware of the temptation to ask more and more services from regulatory agencies, since this inevitably leads to bigger budgets, larger staffs, and more power for these agencies.

The public must demand an end to the senseless proliferation of regulatory demands, such as the chauvinistic repetition of animal tests or controlled trials that have already been impeccably performed elsewhere.

Current regulatory demands need to be carefully scrutinised to determine which are cost-effective; those that are not should be deleted.

The public must realise that a healthy, vigorous, competitive, innovative drug industry is not an evil, but a social necessity.

In developed countries, at least, the public must insist on a continuing national commitment to both basic *and* applied research, without which pharmaceutical progress will stop. This means expenditure of both federal and private monies.

I suggest that the public will not do *any* of these things unless we take the initiative and inform the public by every means at our disposal. The media and the politicians are often remiss, but I refuse to believe that they suffer from invincible ignorance. Things will not improve if we whine and mutter in our cellars instead of shouting from the rooftops. The public must be aroused from its dogmatic slumber before it is too late, and they are best awakened, in my view, by enlisting as shock troops in the battle academicians, physicians, disease-oriented foundations and the sick and their families. The drug industry cannot do it alone, because they are suspect in the eyes of many and not the most effective educators of the public.

The problem is simple to state, if not easy to solve. Does the public want new and better drugs, or not? If it does *not*, the present situation requires very little change, since the ambience will, by the year 2000, be just about perfect for achieving that goal.

But if the public *does* want new and better drugs, *if* it is frustrated by diseases and symptoms that are imperfectly controlled by our present drugs, the climate will have to be changed.

Medicines and the economics of medical care

Ingemar Stähl
Department of Economics, Lund University, Lund, Sweden

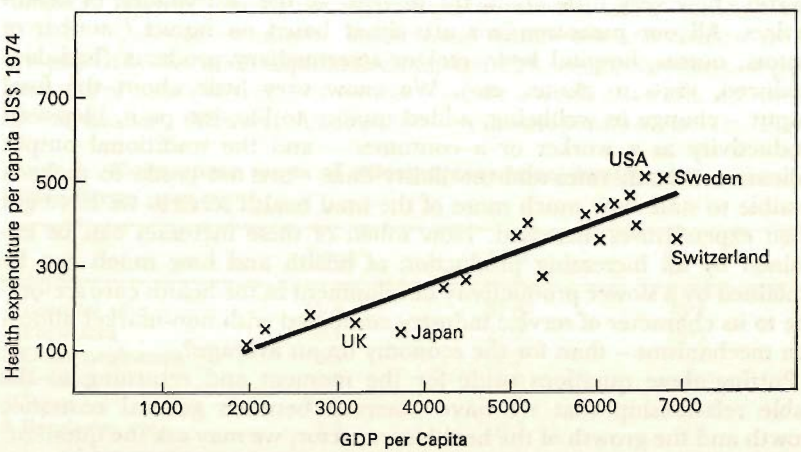
1 Introduction. The growing health care sector

During the last decades all industrialised countries have experienced a fast growth in the expenditures for health care. In the developed countries the share of Gross Domestic Product (GDP) spent on health care varies between 4 and 7.5 per cent. An average for the typical OECD country is 5.7 per cent. We will find the United Kingdom somewhat below the average with a share of 5.2 per cent while countries such as Sweden, United States of America, the Netherlands and Denmark are above 7 per cent.

If data on GDP per capita and health care costs (private and public expenditures for consumption) are brought together in a diagram (Figure 1) we will find that it is very easy to construct a straight line through the dots. Using the language of econometrics we can say that the relationship between GDP per capita and health care costs per capita will explain about 90 per cent of the variations on outlays on health care between countries. Rich countries can spend more on a commodity such as health care, which thus can be said to be income-elastic.

All the different methods of planning and institutional frame-works in the industrialised countries can thus be summarised into a very simple rule: when incomes (GDP per capita) rise by 1 per cent, health expenditure will rise by a little bit more than 1 per cent, or to be more exact 1.2–1.3 per cent. This is the result we get in a cross-section study of countries at one point in time (1974). But it we apply the same reasoning to the development of health care over time in different countries we will reach similar results: in the year 1962 the average share spent on health care in

FIGURE 1



the OECD countries was 4.1 per cent. The growth to 1974 can then be interpreted as an income-elasticity of about 1.4, ie, when incomes grew with 1 per cent health expenditures grew with 1.4 per cent.

Analysis of this type brings us far away from concepts of need, which has become so popular in the medical discussion. In a society with considerable wealth many or all really basic needs could be fulfilled with a small share of the present consumption levels. Our consumption of food, clothing and housing, just to mention some areas basic for survival, has long ago left a level where we could apply simple or basic need concepts. We have to learn a similar lesson when discussing the growth of the health care sector. For an economist it is not at all astonishing that some of the traditional indicators of the effects of medical care, eg, death rates, no longer respond to the increase of resources spent. As for most other consumption the purpose seems more to be to add life to years and not years to life. In any case it is not obvious that we should apply stricter standards to our medical consumption than to other parts of consumption in the rather affluent societies of the western world.

But this does not mean that allocation in the health care sector is without problems. In a sector without efficient pricing and with zero user charges – many of the economist's traditional yardsticks when measuring efficiency have disappeared. Tendencies of over-consumption induced by the insignificant consumer charges have to be met by systems of administrative controls, rationing and queueing. The traditional theory is profit-seeking firms have been turned into what is probably size-maximising hospitals and administrations without any contact of the price system with the consumers' preferences. Strong professional organisations exert considerable monopoly power. This is a little bit of the sheltered domestic oriented, non-profit environment in which multinational profit-seeking pharmaceutical firms operate. No wonder that there may be some tensions when two basically different economic allocation systems interfere with each other.

2 How large will the health care sector be in the year 2000?

When talking about the growth of expenditures it should be observed that we still know very little about the increase of the real volume of health services. All our measurements are either based on inputs (number of doctors, nurses, hospital beds, etc) or intermediary products (bed-days produced, visits to clinics, etc). We know very little about the final output – change in wellbeing, added quality to life, less pain, increased productivity as a worker or a consumer – and the traditional output indicators – death rates and morbidity data – are too crude to make it possible to state how much more of the final health services we have got when expenditures increased. How much of these increases can be explained by an increasing production of health and how much can be explained by a slower productivity development in the health care sector – due to its character of service industry combined with non-market allocation mechanisms – than for the economy on an average?

Putting these questions aside for the moment and returning to the stable relationship that we have observed between general economic growth and the growth of the health care sector, we may ask the question:

what share of GDP will be spent on health care by the end of this century – the year 2000 is the title of the symposium? If the observed relationship will hold for the future we will get a 'surprise-free' estimate that the share will be somewhere between 9 and 10 per cent for the richest countries if they can keep an annual growth rate of about 3 per cent. For the United Kingdom such a mechanical prediction would turn out with a share between 7–8 per cent, ie, about the same share as some of the richest countries have got today.

Shares of this size are completely feasible and realistic and will leave ample space for increases in private consumption of other commodities. The development might mean a moderate increase in the general tax burden, but this is small compared with the total burden of taxes and social security charges that some of the most advanced (ie, advanced with regard to taxes) countries already have. The Netherlands, Sweden, Denmark are already close to or above 60 per cent of the GDP being consumed by or transferred through the public sector. (Sweden will reach a world's record this year with a share around 65 per cent). An increase in the share for health care can thus be carried through without increasing the total tax burden by minor reforms in social transfer systems. But it is also possible that the pressures from other government sectors will be so strong that the introduction of or an increase in user charges will be quite realistic in the years to come.

I will return to the question of user charges or changes in the health insurance system by introducing co-insurance and deductibles later, because this question may be of fundamental importance for the pharmaceutical industry.

3 Behind the trends

Although we can observe stable trends between and within countries there are large differences in the composition of the health sector between countries. In addition, the stable growth process is composed of a development with drastic changes between different subsectors.

On one extreme we will find countries with a high share spent on outpatient care and medicines (Italy and France) and on the other hand 'hospital oriented' countries with Sweden as the most extreme case (Table 1). Medical tradition, institutional framework and relative prices are probably the main explanations for the differences. Sweden is a good example of how a shortage of doctors – partly a result of an efficient policy of the Swedish Medical Association – was compensated by the heavy

TABLE 1 **Component parts of selected countries' health care expenditure (per cent)**

	France	*USA*	*Sweden*
1 Hospital care	41·5	52·8	70·2
2 Physicians	16·1	21·2	11·5
3 Other professions	6·5	2·2	—
4 Dentists	9·9	6·9	6·9
5 Drugs	24·5	10·8	9·1
6 Eyeglasses, etc.	1·5	6·0	2·2

spending on hospitals with all their auxiliary staff.

In an extreme hospital oriented country the share spent on medicines (at consumer price and not producer price) will be less than 10 per cent. Physicians' services – the outpatient part of the system – will take another 11.5 per cent while the hospital part of the system takes more than 70 per cent.

If we turn to physician/medicine oriented countries we will get a drug bill somewhat above 20 per cent. Physicians' services will comprise about 16 per cent and the hospital sector slightly more than 40 per cent.

Even in the most medicine (or rather medicine plus physician) oriented countries the drug bill is a minor and rather stable part of the total health care bill. There also seems to be a rather stable trend of increasing the hospital sector in most countries. Some of the reasons are obvious: new technology such as renal dialysis, brain and body scanners, by-pass operations are hospital oriented. The growing share of the population that is very old explains parts of the increase in long-term care – but only parts, because here we have an area where supply always will find demand if user charges are zero. Increased participation of women in the labour market will also strengthen the pressures of institutionalising the care of the old disabled persons. Another important factor behind the 'hospital explosion' is probably that surgery now is performed on much older patients than previously, with resulting increases in average stays.

It is a kind of conventional wisdom among economists that productivity growth in the health care sector is very slow. This seems to be a general experience from service sectors where returns to scale are limited and where increasing wages can only to a small degree be compensated for by more physical capital. The possibilities of introducing labour-saving physical capital in the long-term care are rather limited and much of the physical capital introduced in the hospital (surgery oriented) part of the system has mainly been quality improving and cost increasing.

But this conventional view neglects the productivity changes connected with a complete change of technology. It is true that a conventional way of increasing productivity is not open to service production, eg, an opera performance. It is not possible to play *Cosi fan tutte* five per cent faster each year or substitute ten violins with one much larger and capital intensive violin. If the wages of the singers and musicians are to follow the general wage rises we will expect opera tickets to become increasingly more

TABLE 2

Part of the care system	*Important factors of production*	*Productivity development/ price development.*
Out-patient care	Doctors – human capital intensive	Increased wages
	Medicines	Decreased prices
Hospital care ('cure')	Labour with a mixed composition of skill capital	Increased wages
	Physical capital	Stable or decreased prices
Long-term care	Labour with a lower level of skill capital	Increased wages

expensive over time. But completely new technologies – records, stereo equipment and television – make it possible to transmit the essential parts of an opera at a fraction of the costs of attending a live performance.

Probably we cannot expect to increase the productivity in long-term care in the future. But from the past we know many examples of drastic productivity changes in medical care, mainly connected with the introduction of new drugs or vaccines. In a discussion of past and future tendencies it will be appropriate to distinguish three technological levels (Table 2).

A large part of development in the health sector can be described as moving the treatment of a specific disease between the levels described in the table. Tuberculosis was once a long-term care problem but the introduction of mass screening, surgery, vaccination and finally chemotherapy changed the whole character of the treatment process.

It is easy to find many other examples from the past of these technological transitions. Poliomyelitis had not only a high mortality rate, but there was also no cure for the permanently disabled. In extreme cases life could be prolonged only by use of respirators. The introduction of vaccination changed the whole picture.

Similar experiences can be found from the treatment of mental illnesses. For some neural diseases we have a process starting with a pure 'care' technology, passing over a not very successful era of neurosurgery, electroshock therapy and finally into a medicine-based technology.

The treatment of hypertension is also an example of these technological shifts. A very large part of the population in the long-term care is there due to illnesses related to a previous history of hypertension connected diseases. By preventing strokes, quality of life can be immensely improved at the same time as costs may even be decreased. In this case it is interesting to observe that the intermediate neurosurgical technology (due to its dangers) could only be used in extreme cases of hypertension and was rather soon phased out with the introduction of a number of generations of drugs. Each generation had less side effects and thereby moved the borderline for high blood pressures that could be efficiently treated continuously downwards.

For the future we can distinguish between three different tendencies regarding productivity development:

a Mainly cost-decreasing medicine related therapies, partly substituting hospital treatment or long-term treatment

b New cost-increasing therapies, cf, the technical possibilities of surgery at high ages

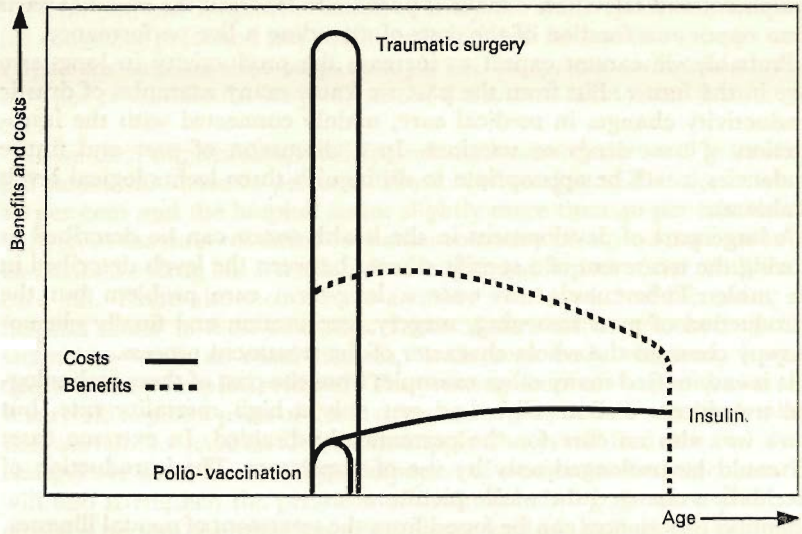
c A constant productivity in long-term care with increasing relative prices.

In the past a typical pattern for the benefits and costs of medical treatment can be described by the following diagram (Figure 2).

Benefits ranged over a considerable time span. At present much of the expansion of the health care sector is directed to the treatment of old and very old patients with a limited life-span for the benefits and considerable costs.

Effective treatment at an early age will increase the number at risk at a higher age. As life is obviously not eternal and we have a natural ageing process determined genetically, we will get into a situation in which there

FIGURE 2



will always be a 'next' disease or chronic ill-condition for every disease that can be effectively and efficiently treated. We can raise the important question if there is a final limit for what can be spent on long-term care as more and more individuals will approach their genetically determined maximum ages.

If we can treat cancer, a disease where a medical breakthrough still will have a considerable impact on remaining years saved as well as relieving pain, uncertainty and tragic events at middle age, we will probably be left with circulatory diseases as the main cause of death. But if improvements are achieved in this area, what will then be the next? Senile dementia – a disease with considerable long-term care costs? Or can we achieve sudden death at a high age without long periods of previous disablement and hospital care?

4 Medicines in future health organisations

As was indicated earlier there are large differences between countries regarding the composition of the health care sector. We still need much more research to understand these differences. Are they explained mainly by basic epidemiological differences? Or is it possible that wellbeing with regard to medical consumption can be produced with a high degree of substitutability between hospital care and out-patient care? Is the solution perhaps so simple that I feel equally well if I can see a family doctor three times more per year for rather trivial diseases or if I am allowed to have a complicated operation with an uncertain outcome at high age? If the main task of marginal resources spent on health care is to relieve pain and uncertainty the first alternative may not be a bad choice.

How much can we explain by relative prices, reimbursement rules and insurance institutions or by medical traditions? It is reasonable that (with the price development in front of us, with increasing real wage costs and

decreasing real drug prices) the optimal mix between hospital care and out-patient care should change with an increase in the volume of services produced in out-patient care. (This may, however, still imply that hospital care increases its share because of the unfavourable price development.) Relative price development will also favour different types of self-treatment and self-medication. Specific development of drugs – or rather drug preparations – that are suitable for self-medication may thus be a possibility for reducing the total health care costs.

We know that there are already existing drug treatments that are good competitors with surgical treatment. At this conference some of them have been mentioned: Chenox to dissolve gall-stones and Tagamet for the treatment of ulcers. We have the very interesting discussion of by-pass surgery versus drug treatment. These examples also have in common that they are innovations with importance for the health care organisation, eg, a full use of the drug therapy will decrease surgical departments and increase outpatient care. But we know very little about how bureaucratic organisations accept changes of this type and what resistance that can be mobilised from the shrinking parts of the system. I also think that it is necessary to look upon the marketing efforts of drug companies in this context. A large part of the marketing is devoted to the introduction of new drugs and new therapies into a bureaucratic system with possibly small incentives for internal structural changes.

I have earlier stressed the importance of not over-estimating the value of mortality statistics. Although progress might be considerable in treating the two main killers at a pre-senile age – cancer and heart diseases – we should not forget that mental disorders still are a very heavy burden for the health care bill. For most countries 15–25 per cent of the hospital costs are spent on mental disorders. Rheumatism is not fatal and does not lead to high hospital costs, but it is still a very large item on a social health bill including earnings lost and decreased quality of life.

Finally I want to raise a special point. With the increasing costs for health care, there has been an increasing interest from governments during recent years to exert more control. Mainly two different approaches are discussed:

a Introduction of deductibles and co-insurance in the health insurance schemes, ie, having the reimbursement system and introducing non-zero user charges.

b Stricter budget controls and more explicit rationing of 'free' services.

The problem is that these controls will probably change the relative prices consumers and physicians will experience. It is very easy to get into administrative controls which distort neutrality between prices and different factors of production. The recent German experience is a good example of how short-term budget controls may have long run effects in discriminating against the use of medicines. We can already observe that medicines generally are less subsidised than other factors in the health sector. Pharmaceutical companies should probably be more aware of how the total health care system, including the social insurance system, affects the demand for drugs. In the future these problems may be of the same or of greater importance for the industry than price control and regulation are today.

Medicine in the year 2000: an optimistic forecast to AD 2000

G. E. Paget MD DCH FRSE FIBiol
Director, Inveresk Research International

When Mr Teeling-Smith raised with me the possibility of my contributing a paper to this symposium, generally dealing with a view of medicine in the year 2000 through rose-coloured spectacles, he suggested that the basis of the consideration should be a 'Mini-Delphi' study. To this end, I concocted an elaborate questionnaire and invited a large number of people, whose views of the future I thought likely to command both my interest and respect and that of this audience, to answer these searching questions. In retrospect, not surprisingly, the response was rather small and ranged from a close friend who said:

'This questionnaire strikes me as phoney nonsense. After several determined attempts I still find myself unable to bring myself to participate in such a clearly time-wasting exercise.

'By returning the questionnaire in its original "virgin" stage I hope you may be able to send it to someone more sympathetic to the whole concept. Please forgive my apparent lack of collaboration. I am sincerely horrified at the futility of the exercise.'
(Professor Eric Horton)

To a number of individuals who conscientiously attempted to answer the whole questionnaire to the best of their insight and knowledge, to all those who responded in whatever manner to the questionnaire I am extremely grateful. To those who found it either burdensome or incomprehensible or foolish I apologise.

Unfortunately, the number of respondents was so small as to make any analysis of their response of less general interest than I had hoped and therefore I have chosen, rather than to present such an analysis, to attempt my own predictions, making reference when relevant to any particular consensus revealed by the respondents who answered the questionnaire.

It is, however, first worth enquiring whether such criticism as I have quoted – that attempts to extrapolate into the future, present day technical trends are worthless and time wasting – is valid. Certainly in other fields of endeavour such attempted extrapolations are not disregarded and I have recently read a study of the design, operation and economic impact of an advanced commercial fusion reactor, although sustained power yielding commercial atomic fusion has not been achieved in any sense at all.*

I have long thought that it would be interesting to establish a speciality

*This statement was valid at the time it was written, but since August 1978 may have become invalid.

of retrospective futurology to analyse from past predictions in any technical field the extent to which they were borne out in the event. Many of this audience will recall the confidence with which in the late 1940s and early 1950s it was predicted that chemotherapy of viruses by extension from chemotherapy of bacteria would appear within a few years and the disappointing extent to which that prediction has failed of fulfilment. Equally in those times it seemed unlikely that, because of its essentially obscure nature, mental disease would be brought within the ambit of pharmacological treatment, whereas this has been one of the striking areas of success of modern therapeutics. Predictors therefore, must beware on the one hand of an oversimplified approach to a biological problem and on the other hand must allow for a certain random serendipity in some unexpected areas. Prediction – or more respectably extrapolation – is thus fraught with problems. However, if no attempt to look into the future is permissible then extraordinarily optimistic or pessimistic feelings will, uncontradicted, rule the day. In passing we should note the baleful effect of certain predictions, especially those made by marketing experts, who are usually completely unable to accept that a new medicine may create a new market and would prefer to have the fiftieth analogue of Librium to a completely novel pharmacological agent.

In many ways, the year 2000 is too close for completely untrammelled predictions even although it is the year in which I, if I survive, shall be 78, and shall have spanned the period from the virtual impotence of medicine against most major diseases, to the time now under prospective review. My own father died, in the prime of life in 1931, of primary pneumococcal lobar pneumonia – an event of unimaginable rarity nowadays. I say that it is too close because of the long and increasing period over which drug development now must extend. To be making a serious impact upon practitioners of medicine in the year 2000 a drug must, one supposes, have been introduced in the year 1998 or thereabouts, at the latest.

Most members of the pharmaceutical industry would agree that the lead time from starting a research programme from scratch to achieving a successful marketed drug is of the order of at least 10 and more likely 12 to 14 years. It can thus be seen that drugs that will make a significant impact on the practice of medicine in the year 2000 will be the result of research programmes now in being or to be started within the next handful of years. They are therefore at least conceivable in intellectual terms at the present time. Any fundamental new scientific discoveries will only affect the discovery of drugs to be introduced post 2000.

For obvious reasons, the most promising and interesting research programmes of the pharmaceutical industry are amongst its most closely guarded secrets. However, the reason that this is so, that is, the need to obtain and preserve a commercial advantage by directed research, also enables us to make some predictions about likely areas of significant advance. This statement is based upon the premise that success in general follows the big battalions nowadays and that attention of pharmaceutical research is predominantly directed towards those markets that offer prospects of large commercial returns. It is also the case that over the last decade or so at least, pharmaceutical research has to a considerable degree abandoned the random screening approach that – however success-

ful in turning up leads or even commercially viable drugs – is essentially anarchic and unpredictable, in favour of a reasoned approach based upon greater insight into the biological interaction of drugs and disease processes. In a sense this is of course a return to the earliest days of chemotherapeutic research when scientists believed that science would succeed and before the importation of the age of scientific mediocrity that contaminated so much pharmaceutical research in the 1950s and 1960s and thereby caused the abandonment of this intellectual belief for the less rigorous glamour of the roulette wheel.

You will note that I have so far only spoken of pharmaceutical research and I think that there will be few here who will challenge my implicit assumption that the major influx of new drugs will derive from work in the pharmaceutical industry. Academic investigations will contribute some new products, especially in the fields where large teams and major investment are not required but if academic science makes its proper contribution to the progress of medicine, it will be concerned with generating ideas that will in turn serve as the basis for the discovery of drugs to be introduced in the early decades of the next century.

We may begin, therefore, to be able to define some of the characteristics of the new medicines that will be of importance in the world of 2000. They will be concerned with diseases of major importance. They will be the result of knowledge already existing and its immediate extensions, rather than knowledge at present completely inconceivable. They will be discovered by rational processes rather than by a random activity, and often enough they will first be defined in terms of some biological action rather than as a cure for some specific condition – they will be drugs in search of a disease, as Dr J. W. Black, the most successful drug innovator of our generation, once put it.

It is undoubtedly the fact that those susceptible to scientific glamour – and that is perhaps most of us – will begin to think of the enormous amount of scientific effort being directed into the areas generally called molecular biology, although this is now so large a subject that one wonders whether some more precise subdivision of the general area is not about to occur. I suppose that to most of us relative laymen the glamour area of molecular biology is the rapid progress that has been made in recent years unravelling the genetic code and illuminating how the genetic material comes to direct the character and function of cells and organs.

Indeed, so active has this area become that political and other non-scientific activity has been directed towards it (activity which at least from the outside seems to have been largely ill-judged and irrelevant). However, it is clear that a number of organisations whose prime intent is to discover biologically useful substances are making a very considerable investment in this area and it must be supposed that some at least of their investments will result in therapeutically useful substances.

I doubt whether in the time span of which we are speaking the really far-out possibilities that are mentioned in some critiques of this area will come to be achieved. I do not think that we shall come to see the development of carrier viruses that will implant deficient genes into human beings as a part of medicine in so short a time. I do not think that 'one-shot' curative therapy for any genetically mediated disease will be available.

However, I do believe that the increasing understanding of the mechanism of action of genes at the cellular level will enable the design of more conventional drug systems to be achieved that will intervene in the defective process in a favourable way and it may be that diseases such as phenylketonuria and retinitis pigmentosa, for example, will yield to this approach. It may well be that methods of manufacture of human hormones such as insulin and others will be achieved microbiologically by genetically modified micro-organisms. It is also from this area of molecular biology that possible approaches to virus chemotherapy as opposed to immunisation will be derived since it seems clear that intrinsically similar mechanisms and methods of investigation are involved in virus disease as in genetic defects. It would be surprising and disappointing if even by the year 2000 we have still failed to achieve at least one completely effective and relatively non-toxic treatment for a major virus disease and I confidently predict that one such at least will be in use. In this connection it is interesting to note that emergence of compounds that, while not directly therapeutic seem to confer immune competence on the treated organism, and perhaps this piece of serendipity may be the opening of a whole new class of therapeutic agent. Another branch of molecular biology now so well established as to seem conventional is the understanding of the structure/function relationships of proteins of biological importance. Understanding of the structure of enzymes and their mechanism of action in this way may contribute to a rational approach to metabolic diseases by substitution therapies more sophisticated than any now available.

Consideration of viruses leads us to the complex area of immunology, auto-immune disease and areas on the border line of virology where so called slow viruses may be involved.

In particular one thinks of course of several major scourges that lie in this general area of pathogenesis – diseases such as rheumatoid arthritis and multiple sclerosis, and many diseases closely or generally related to them. In some of these diseases of course palliation often of a considerable degree is already possible whereas in others such as multiple sclerosis little can be done. It is easy to predict that where palliatives are now available more effective or less toxic ones will certainly be available in the year 2000. It seems unlikely, however, that any fundamental cure or effective prophylaxis for any disease in these groups will be developed since the uncertainty about aetiology and technical difficulties of experimental investigation show no signs of which I am aware of yielding to continuing investigation, at least to such a degree as would lead one to suppose that a clear line from concept to drug can be drawn. Other aspects of immunisation of course will flourish and there can be no doubt that vaccines for common diseases at present not preventable by immunisation will become available. It is surprising that one of the greatest points of agreement of the small panel who answered the questionnaire, was the likelihood of the development of effective vaccines for sexually transmitted diseases, and it is known that many other diseases are under investigation with the end point of vaccines in view and cytomegalic virus and respiratory syncoetial virus will perhaps yield to immunisation before the year 2000.

One wonders whether determined vaccination campaigns will succeed completely in eradicating any pathogen in the way that smallpox is from

time to time reported – I think to date always incorrectly – to have been eradicated. It will be an ironic comment upon humanity if the only species that it can succeed in rendering extinct are the large, the beautiful and harmless, and perhaps itself, while the small, malignant and useless survive all assaults upon them.

It seems highly likely that the chemotherapy of bacterial disease will continue to improve and again there was a high degree of agreement among my respondents that more effective, less toxic drugs, less prone to produce bacterial resistance will be developed.

Another area of considerable agreement among my respondents is that of contraception. Nobody can doubt that the final answer to the ideal contraceptive has not yet been developed and neither the Pill in all its forms nor the IUD is regarded as being the final answer, especially since the best contraceptive advice is to vary the method used fairly frequently. This implies a choice of contraceptives wider than is at present available. Again I would predict with considerable confidence that at least a 'morning after' contraceptive will be developed and that there is considerable likelihood of a male contraceptive being developed, since studies of such agents have been in progress for a very long time. In parenthesis of course, one should say that the validation of such innovations and in particular, the demonstration of their freedom from carcinogenic and genetic ill effects as well as their potential reversibility, pose very complicated problems and a substantial fraction of the 22 year span to the year 2000 will be required to solve them even if useful alternatives have already been defined.

Turning to more speculative areas, one cannot ignore the enormous use of psychoactive substances for mood change rather than for the therapy of defined disease. Tranquillizers, anti-depressants, sedatives, and stimulants have been a major force in therapeutics and indeed in socio-pathology over the past few decades, nor is this new since alcohol, tobacco and, in some societies, marijuana have been used for this purpose for centuries. It seems highly likely that more specific psychoactive drugs will be developed purely for the modification of mood and intellectual processes generally and that it is likely that some such substances will be approved for general non-prescription use by the year 2000, since it would not be difficult to find substances more innocuous and controllable and more adequately studied than the triad I referred to earlier. A well-studied substitute for tobacco would be an enormous advance in the prevention of major diseases. In parenthesis again, I should say that marijuana comes nowhere near meeting the specifications for such a substance since it appears to be at least as toxic and probably greatly more so, than tobacco and the ill-informed who press publicly to have it legalised would in my view, if successful, institute a major catastrophe comparable to that perpetrated by Sir Walter Raleigh 400 years ago.

I have said nothing specifically about the problems of the third world although the charge levelled at the pharmaceutical industry by its critics usually includes the allegation that it pays no attention to those problems. This is quite simply not true and enormous sums have been spent by the pharmaceutical industry in seeking treatment for diseases predominantly affecting the developing countries of the world. In some areas it is pro-

bable that material advances will continue to be made and the more effective therapy of leprosy seems certain to be developed, and is incidentally another area in which some agreement among my respondents was found.

Other diseases such as filariasis and schistosomiasis have resisted very great attempts to find treatments for them. The reason for this has always puzzled me since one would suppose that large parasites of complicated and alien biochemistry would be extremely susceptable to chemotherapeutic agents. This has proved not to be the case, however, and one must wonder whether these parasites will yield even in the next 22 years or so. It is perhaps cynical and callous to wonder whether the economies of the developing nations could support a very large increase in the life expectancy of the population, if at the same time they failed to take steps to limit that population in a realistic way, by adequate birth control methods, and fundamental social reorganisation upon which successful birth control policies must be based.

In mentioning the third world it would be purblind not to recognise that medicine is the least of its problems and indeed, as I have mentioned above, successful medicine might even be a curse rather than a boon. The problem of the developing world now and in all probability of all the world by the year 2000, will be the overriding problems of food and energy. If the predominant medical problems are not to be those of trauma and radiation sickness, the problems posed by diminishing energy supplies and disproportionate distribution of food supplies must be solved. The callous folly of developing drugs to administer to those whose prime need is protein is obvious. It is obvious also that alternative sources of protein must be sought and developed with great rapidity, not only for the developing countries and Africa and Asia but in all probability for those of us who have been more fortunate so far. To some extent the technology required for the development of these new food resources parallels that required for medicines and, like the pharmaceutical industry, one may expect the new food industry to be an offshoot of established chemical giants.

One has but to look around, and indeed no further than at the speaker, to realise that the current problem of the western world is of over-nutrition, at least at the present time.

A true appetite controller has yet to be developed but a side-effect-free means of readjusting downwards the appestat would be of enormous use and is no doubt the subject of research in very many pharmaceutical laboratories. It seems likely that for those of us in the year 2000 who are still able to over-indulge in food such a drug may well be available.

It is not a complete *non sequitur* to say that a very high proportion of western men will die because of the inappropriate clotting of their blood, particularly in their coronary and cerebral circulations. This major cause of mortality is surprisingly little the subject of pharmaceutical research in the United Kingdom, whereas I am in a position to say that it is a major subject of research in many of the largest pharmaceutical companies in other countries. It is highly likely that one or more of these companies will in the next few years be in a position to introduce striking new drugs for the prophylaxis of thrombotic disease. Incidentally, it would be ironic if the prospective Oxford Study of aspirin should demonstrate that this much

maligned *wunderkind* was in fact a complete answer to thrombosis prophylaxis.

I suppose there is no more frequently asked question of a medical research worker by a lay person than, 'How soon will there be a cure for cancer?' The naivety of this question as posed is obvious to anyone with a nodding acquaintance with research in this disease complex, and I think no one now expects there to be a single wonder drug or even group of wonder drugs that will do for cancer what the broad spectrum antibiotics to a considerable degree have done for bacterial infection. Nevertheless, it would be disappointing and surprising in the highest degree if the vast sums of money that have been spent on cancer research in recent years failed to produce any significant result at all, and one must therefore predict that over the next 20 years more efficient chemotherapeutic agents for the treatment of particular cancers will be developed. It is worth noting, however, that probably the biggest advance against the neoplastic diseases must be expected in the field of preventive medicine. I have already pointed out the boon that would follow either the complete cessation of tobacco smoking or alternatively the smoking of safer materials. It seems highly probable that other major environmental causes of cancer will be identified and in consequence much cancer will be avoided. The great strides being made now in evaluating the safety of environmental chemicals must have a positive effect on the incidence of cancer and perhaps even within the time scale of which we are speaking.

Another area that excites the public interest disproportionate to its importance in the general practice of medicine is that of organ transplantation. Despite its present limited impact on the totality of human diseases, enormous strides have been made in the past few decades and anyone active in medicine 22 years ago would probably then have scoffed to believe that kidney transplantation would become the commonplace successful procedure that it now is. It is certain that improved immunosuppressive drugs and improved methods of tissue typing will enable this progress to continue during the next 22 years. We may doubt whether the transplantation of human hearts will have been worth the enormous diversion of resources from more mundance activities but we cannot doubt that it will continue if only because, like Everest, the problem is there. I cannot think, however, that it will be in the period we are discussing more than a surgical *tour de force*, performed like some stage illusion at a few selected centres.

However, a more helpful area is, I am sure, the development of more elaborate prostheses. Here the development of micro-processor chips must make feasible the development of highly programmed substitutes for many natural functions. Since, as I understand it, such microchips need very little current to activate them, it may well be that even within the 22 year period reviewed fusion of biology with solid state physics will make available limb prostheses indistinguishable in function, and perhaps even superior in function to the natural limb, and more remotely one can well imagine the principle being extended to any mechanical or sensory function. Incidentally, one should not ignore the inevitable improvement in joint prostheses so that in all probability by 2000 the complete replacement of manual and some spinal joints will occur.

I have but touched in the foregoing paper on the areas where the more spectacular advances are likely to occur. I would not wish at all to decry the steady improvement that will undoubtedly happen through minor modifications of existing drugs and in the convenience and safety of much standard medication. Non-sedative anti-histamines and analgesics, non-addictive sedatives, less toxic cytolytic agents, safer intravenous anaesthetics and a whole host of other agents will undoubtedly appear – sadly, I fear, to a chorus of 'tut tut' from the academically minded who do not happen to suffer from the diseases benefited by these relatively minor advances.

I have not touched either, upon the more intelligent use of drugs by the medical profession although this of itself would be a major therapeutic advance. All these things will no doubt happen almost unnoticed and it is not unreasonable to hope that at least a proportion of my more spectacular predictions will be fulfilled and that serendipity will allow us to stumble upon other therapeutic successes.

In case you should think that in donning rose-coloured spectacles I have completely lost touch with reality I would like to end on a more sombre note. All that I have said presupposes that major companies will continue to engage in pharmaceutical research because success in it gives rise to protected profitable specialities. We are however at danger to 'kill the goose that lays the golden eggs' and one of the most disturbing things I have seen recently is the slide shown by Dr Cromie based on data for the world's largest pharmaceutical company. The extrapolation is clear that if present trends continue this company at least will have ceased meaningful pharmaceutical research by 1988. It may be therefore that the year 2000 will be the pinnacle of the pharmacological revolution and that from then on the path will lead downhill.

Epidemics of the future

George Teeling-Smith MPharm BA FPS
Director, Office of Health Economics

In this final paper of our symposium, I intend to return to the opening theme on the contribution of modern medicine to health care. I shall do this first by looking at the nature of epidemics and some of the factors which can cause them. This will lead naturally into a discussion of the well-established concept of health as a balance between the wellbeing of mankind on the one hand and the challenge of his essentially hostile environment on the other. Against this background, I shall discuss the objectives of health care in a historical context.

Finally, from all of this I shall try to draw out the main threads in the arguments which have developed over the past two days. These involve the conflicts which are inherent in the simultaneous development of technological innovation, man's natural desire for an expression of individuality and the insidious growth of State bureaucracy. I should warn you that the picture which emerges is a complex one, but nevertheless it is not one which introduces new arguments.

Looking first at the definitions of epidemics and illhealth, one thinks instinctively of the emergence of dramatic episodes such as the bubonic plague of the middle ages and tuberculosis resulting from the industrial urbanisation of the nineteenth century. However, there are many different ways in which epidemics may occur. Sometimes the origin of such epidemics is obscure, as has recently been the case on a small scale with 'Legionnaires disease' in the United States. In other cases, there have been epidemics which have spread from animals to man; here anthrax, rabies, psitticosis and again more recently Marburg or 'green monkey' disease are obvious examples. However, perhaps the most common cause of epidemics has been the geographical spread of known human diseases to new regions. Syphilis in Europe is thought to be such an example. It was apparently brought to Spain from the Americas in the fifteenth century by Christopher Columbus' sailors. In more recent decades, tuberculosis and measles have spread rapidly amongst some non-immune populations in rural Africa. In this case, the bacteria and viruses were brought to the villages by natives returning from the infected townships.

This introduces the first important principle to emerge in this paper. For individuals, contact with a disease may cause either clinical symptoms or symptomless immunity. Which of these alternative paths the disease follows is the resultant of two factors. The first is the virulence of the causative agent. The second is the immune or protected status of the population and the individuals within it. This is the principle which Macfarlane Burnett has so eloquently described in his book on *The Natural History of Infectious Disease*.[1] Taking the case of tuberculosis in Victorian England as an example, almost all urban dwellers were exposed to the tubercle baccillus which had become endemic in the towns and cities. Once the infectious agent was concentrated within these newly

urbanised populations its virulence increased and about one-fifth of those exposed to it developed clinical disease and (in the absence of antibiotics) almost invariably died. However, the other four-fifths of the population developed no observable symptoms from their infection with tubercle and merely developed immunity against subsequent exposure to more or less virulent strains of the baccilli. This example is my first illustration of the concept that good health depends on achieving a satisfactory balance between man's defences and the various hostile agents which attack them.

Another striking example of how a previously widespread and benign infection gradually became a virulent epidemic was with poliomyelitis, first in America and later in Europe. In the generally unhygienic environment of the nineteenth century, the poliomyelitis virus was endemic and infected the great majority of people during infancy or early childhood. At those ages it caused little damage. However, as principles of stricter hygiene were introduced, the infection became less prevalent and many children reached adolescence without having already been infected by the virus. When the disease struck at this later age, it frequently caused paralysis or death. The dramatic epidemics of poliomyelitis of the 1930s and 1940s were the consequence.

Another different, although in some ways similar, case is with bilharzia in parts of Africa and South America. Here modern irrigation has made the vector snail so common that practically all agricultural workers contract the disease. For the present, programmes of eradication using modern medicines are virtually doomed to failure, because re-infection is so rapid as to make them almost pointless. However, once again a stage will be reached where the vector snails can be sufficiently controlled so that bilharzia becomes a treatable epidemic rather than an inevitably endemic state.

This shift from the state in which a disease is so common that it is locally considered 'healthy' to be suffering from it to one where it is seen to be a clearcut 'disease' justifying treatment has further important implications. If neither simple diagnosis nor treatment exist for a condition, and if it is reasonably widespread, it will not generally be regarded as a disease. Thus departing from the examples of infectious diseases which I have been dealing with so far, one can look at the present rise in the prevalence of relatively minor mental illness as another case in point. Eccentricity, severe anxiety and depression were probably so commonplace in the past that they were taken as 'normal' – especially in old age. Now such states are no longer so readily tolerated by the individual and his family. They are also very generally amenable to pharmacological treatment. Thus, they are now thought to be 'abnormal' disease states and are often diagnosed and treated accordingly.

In this sense, modern medicine not only provides more or less simple cures, but also tends itself to create 'epidemics'. This is because modern medicine is steadily producing diagnoses and treatments for states of 'illhealth' that have hitherto been untreatable and hence accepted as inevitable. By producing efficient diagnostic methods and effective therapies, these states of illhealth have become diseases to be treated. Thus an unrecognised endemic condition or an apparently rare eccentricity can in less than a generation become a medical epidemic in urgent need

of treatment. By contrast, of course, the development of the anti-tubercular drugs in the 1950s suppressed the epidemic which had been created by urbanisation. Thus therapeutic progress can have two apparently conflicting roles in health care. But both in the broader sense represent real progress towards the wellbeing of mankind.

The example of the modern neuroses and the depressions leads on to another way in which new epidemics may occur. This is simply by defining a particular situation or pattern of behaviour as being a sickness. Thus disease can be created simply by a change in social attitude or even in administrative regulations. For example, alcoholism and other forms of drug addiction have emerged in the twentieth century as new 'diseases', although certainly drunkeness and dependence on other drugs were more prevalent in previous centuries. 'Childbashing' is another example where it is almost certainly social attitudes and awareness rather than the mothers' behaviour which has altered.

The important point is that the principles which have been expounded so far do not apply only to infectious or to psychological illness. The introduction of cigarette smoking, the use of carcinogenic agents in industry, and the introduction of the motor car are all cases where man himself has introduced new hostile elements into his environment. In such cases, he has had either to cope healthily with the challenge or else to succumb as a diseased victim. Similarly the scourges of coronary heart disease and cardiovascular accidents are the result of individuals having failed either to live a healthy enough life or to have been strong enough to withstand the stresses and strains which they have imposed on themselves. Further, as expectations of good health expand, conditions of illhealth appear to become more prevalent.

All of this illustrates the fundamental principle that in the final analysis good health depends on being born with or developing sufficient resistance to cope with the challenges of the environment in which one has to live one's life. As the earlier sessions indicated the role of chemotherapy and pharmacology has simply been to help man to tip the balance in favour of his survival and wellbeing so as to prevent him from succumbing to the hostile elements which he faces. This role is perhaps seen most clearly in individual cases with the antibiotics and other antibacterials; but it is interesting that more recently the role of cancer chemotherapy is also being seen in the same light. The aim may only be to help the human body to win its struggle against the rogue cancer cells, rather than to eliminate totally the cancer. The concept of 'living healthily with one's cancer' is beginning to emerge amongst oncologists.[2]

The idea of a continuous interaction between man and a hostile environment is, of course, by no means new. Rene Dubos in his 1965 book, *Man Adapting*, pointed out that a healthy life has always consisted of maintaining a good balance in this sense.[3] Indeed the principle does not apply only to men: all creatures live a precarious existence coping with old and new hazards.

Macfarlane Burnett has nicely described this balance, which is seen in perhaps its clearest form in the 'food chain' concept of wildlife. In this, the herbivores turn vegetable material into animal protein, a proportion of which is subsequently consumed by their carnivorous predators. These in

turn may be killed to provide raw meat for yet another higher group of predators. In this chain, the balance depends on there being sufficient vegetable food for the herbivores and an equilibrium between predators and prey among animals and man. As Burnett points out, this is in practice usually an 'uneasy balance' with the respective populations more often surviving above and below the 'optimum' levels rather than remaining stable.

He gives an example of this uneasy balance from the insect world. When orange trees were first introduced into California, they were seriously affected by a plague of soft-scale insects, which threatened to destroy the orange groves. This imbalance in nature was corrected not by insecticides, but by the introduction of ladybirds, which are a natural predator on the soft-scale insects. As long as there was an abundance of the latter, the ladybirds multiplied rapidly. When their ready food supply dwindled, this multiplication was thwarted. From then on they merely provided a check on the multiplication of scale insects and a consequent protection for the orange crop. In another example, Burnett points out that during Australian 'mouse plagues' the local ibis change their normal diet to one of mice, so as to help the hawks, owls and cats to keep the mouse population in check. He contrasts this with the way in which the Scandinavian lemmings deal with the overgrowth in their population.

More interestingly in the present context, however, Burnett points out that during mouse plagues a large proportion of mice contract infectious diseases. This is, of course, to be expected because, as in the Victorian cities, their large numbers, high density of population and general malnutrition all foster the spread of virulent disease. Nevertheless, this infection of the mice also provides another method of population control. If one takes the 'food chain' analogy one step further, therefore, the mouse tissues provide a diet for the bacteria which are multiplying upon them. On this analogy, man ceases to be the end point in the food chain. The bacteria and viruses and cancer cells can be thought of as consuming man, just as he has consumed both vegetables and meat from other animals in his own diet. On this basis, tuberculosis was aptly named 'consumption' in Victorian times.

This concept of a balance between an individual and his environment can be developed further along the lines of George Pickering's argument in *Creative Malady*.[4] In this he suggested that individuals could develop a disease in order to help themselves to achieve a desired objective. Thus Darwin's persistent illhealth allowed him to withdraw from normal social activity and to concentrate exclusively on the development of his theory of evolution. In much the same way, a child who detests a particular subject at school may regularly become ill on the days when it is due to be taught. The child is literally 'belly-aching' about his own ineptitude at the subject in question.

In the case of creative genius, illhealth may be an acceptable price to pay. However, in the case of the schoolchild, the avoidance of unpleasantness in class by the development of psychosomatic symptoms is an obvious maladaption which could become progressively more troublesome and counter-productive if not corrected.

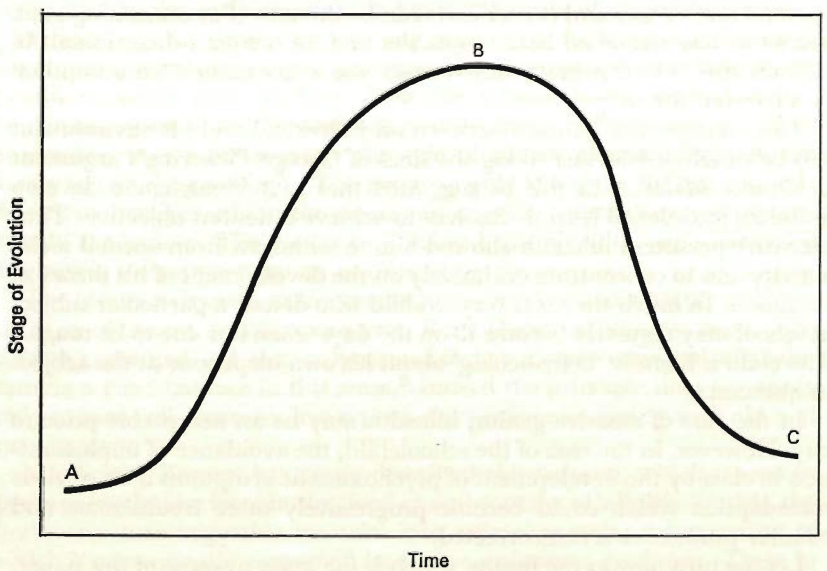
Let me turn now to the future, which is the main purpose of this paper.

When one considers bacterial, viral and protozoal infections, there seems to be relatively little risk of major epidemics from entirely new organisms. The examples of 'Marburg' and 'Legionnaires' disease illustrate how the very sophisticated international public health services can isolate and eradicate a 'new' infectious disease. On the other hand, of course, if one or other of the major world powers – or more possibly a rogue nation with sophisticated science and inadequate political sense – were to take deliberate steps to indulge in germ warfare the situation would be different. But such an event must be regarded in the same category as a nuclear holocaust and hopefully both will remain no more than remote possibilities.

Similarly, all the indications are that sensible nations will progressively identify and remove virulent substances such as the known carcinogens from the environment. In the same way, potential causes of injury such as the motor car, aircraft, the use of lead and asbestos, as well as new drugs are becoming increasingly trammelled with the paraphenalia of safety. Indeed much of the present symposium has been concerned with the subject of safety of medicines in particular, and the same principles apply to all forms of what has been called 'risk and regret avoidance'. It can even be suggested that an excessive and almost neurotic attention to 'safety' itself constitutes an epidemic.

Let me digress here to show you a typical growth and decay curve, which one of the Economic Advisers at the Department of Health recently christened the 'Teeling-Smith all purpose social and economic model'. This is illustrated in Figure 1. At the time, it was being used to describe the evolution or natural history of the economic costs of typical infectious diseases. Here it illustrates the points which I have made earlier in this paper.

FIGURE 1 **All-purpose growth and decay model**



At point A, the disease is unknown or unrecognised as such and, therefore, incurs no costs. As it starts to spread or to be recognised and diagnosed, it begins to become epidemic and to be responsible for recorded morbidity and mortality which involve costs; in addition resources start to be used in an attempt to prevent and to treat it. With further progress in diagnosis and treatment, its costs rise rather than fall, because with greater awareness of the disease more money is spent heavily on research into its causes and into methods of prevention and therapy. It is only after a certain stage in this technological development that the apogee B is reached and passed, and the costs of the disease start to fall. In due course, more or less complete control of the disease should reduce costs once again back to negligible or zero levels. This is point C. One can think of polio and smallpox as typical diseases which are already at this end of the curve, whereas most mental illnesses are still somewhere around point B.

However, the diagram was aptly christened the 'all-purpose model' because of course it applies to almost all social activity. For example, in the context of this symposium it can be used to suggest the typical evolution of technological innovation, with an initial exponential growth followed by a levelling off of creativity and an eventual stagnation. Certainly for pharmaceutical innovation there is now evidence that government regulatory procedures may have been responsible for a levelling off or even a decline in pharmaceutical creativity. However, the phenomenon is by no means confined to the technology of pharmaceuticals. If in the future neurotic obsession with safety were to get out of control, there would be a possibility that the world could move into some sort of technological 'dark age' reintroducing actual hardship through the inhibition of desirable innovation and through unreasonable restriction on existing technology. As one example, much of the world may already be being denied a potential source of cheap energy because of an almost fanatical belief in the importance of safety in respect of nuclear plants and nuclear materials. The chimera of 'absolute safety' applied in epidemic proportions could do immeasurable harm.

Returning to the diseases, I have already postulated that there is little danger of any major threat from either infections or environmental diseases. To some extent the same is true of inbuilt genetic defects, causing diseases such as early-onset diabetes, where fears that longer survival may produce demographic changes in epidemiology have probably been exaggerated. Similarly, the increasing availability of prenatal diagnosis, with the opportunity of abortion to avoid congenital abnormalities, is another example which is almost certain to improve the health status of the population.

However, against this, there are the indications which I have already mentioned that technological progress itself may in a sense 'create' more illness in the future. As clinical investigation and diagnosis is increasingly concentrated at the cellular or biochemical level, new and potentially significant biochemical abnormalities are likely to be identified. In addition, those which are already known are likely to be diagnosed more frequently. In respect of these inbuilt genetic disorders, epidemiology, biochemistry and molecular biology are still taking us up the steep exponential growth sector of my all-purpose growth and decay model. As so

many people have said in the past, we seem to be in danger of reaching a situation in which a 'healthy' person is simply one who has not had a full enough medical investigation.

But this growth in diagnosed abnormalities is not solely the consequence of more sophisticated diagnostic techniques. It also reflects people's greater willingness to seek treatment for relatively minor maladies and their decreased tolerance of small deviations from 'perfect' health. However, the medical profession and the public must beware in this arena. There are at least suspicions that 'diagnostic labelling' may itself be harmful to health. Multiple sclerosis is a good example here, and one of which many doctors are already sensitively aware. Indeed a recent *Lancet* editorial discussed the role of psychotherapy for those who had been labelled as MS patients.[5] To some extent it brings us back to Pickering's creative maladies. If life is difficult – and whose life does not frequently present problems and difficulties – a respectable diagnostic label can appear to be a refuge from the cruel world.

In this case the human mind and body are 'adapting' in just the sense discussed earlier in this paper; but such a mal-adjustment is properly classified as illhealth. This form of subjective illhealth 'validated' by sophisticated biochemical measurements could eventually present in the form of new epidemics of previously rare and comparatively irrelevant 'diseases'.

In many ways, this could be no more than a continuation of the trend which has already been described. The paradox of dramatic medical progress being accompanied by an apparent increase of illhealth – as measured, for example, by hospital admissions or absence from work attributed to sickness – has already been much discussed. Unless positive steps are taken it seems inevitable that these conflicting trends will continue.

This may not, of course, be an altogether bad thing. Insofar as minor disabilities and discomforts are brought for treatment and are successfully alleviated, there is a real improvement in the quality of life. On the other hand, the possible sense of frustration to which it could give rise is central to the theme of this symposium. It can do nothing but harm to give a patient a diagnostic label in cases where no effective treatment exists. Thus unless medical and pharmacological progress continue to keep pace with the increasing sophistication of diagnosis and with public expectations, the medical and pharmaceutical professions would merely be adding to the store of human unhappiness by continuing to diagnose relatively untreatable illnesses. In this sense, it is perhaps now more important than ever to encourage rather than to stifle pharmaceutical innovation.

This discussion of the possibility of more precise biochemical diagnosis to 'explain' relatively minor symptoms leads onto what is the central message of this paper. This is the interaction between society, medicine and technology.

A little history may be useful here. In the earlier part of the present millenium social structure was largely determined by the Church in collaboration with the traditional feudal system. The limited technology of the times was largely devoted to the glorification of the Church's idea of God, and the principle of an almighty deity was unchallenged. Dating

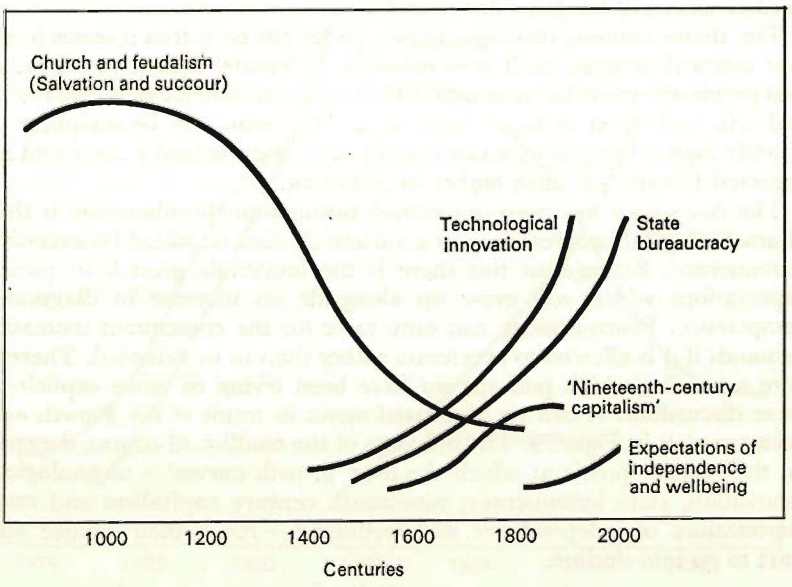
roughly from the sixteenth century, however, major scientific discoveries and corresponding technological advances started to be made.

Partly as a result of these, the natural authority started to shift from the feudal lords and from the Church to codified and bureaucratic state legal systems such as those which followed the American and French revolutions. Perhaps more importantly, economic power started to fall into the hands of what can be roughly described as 'nineteenth century capitalism'. A new middle class emerged both to administer the law and to generate the wealth of nations. Largely as a consequence of the products of the middle-class capitalist economy, by the middle of the nineteenth century there was beginning to emerge a new trend – a public expectation of social and economic freedom based on a greater share in the new national wealth. Schematically, using the principles of my all-purpose growth and decay model, this situation can be illustrated as in Figure 2.

In many ways, medicine developed over the same time-scale in rather similar ways, and is to some extent now in the same state of turmoil as society as a whole. Traditionally, religion, magic and healing were all intermixed with relatively little input from science. Until the last few centuries the teachings of Galen remained more or less unchallenged and the Church not only continued to provide succour and to offer salvation, but could still routinely grant medical qualifications. However, just as social authority started to pass from the Church to the civil authorities, under the influence of scientific and technological developments, so medicine also became separated from its longstanding traditions and from the Church. With the development of medical science in the nineteenth century it started to be based on more sound scientific principles.

In a sense, medical doctrine replaced religious doctrine by adopting the ethic that the maintenance of life was more important than the conditions

FIGURE 2



of that life. By contrast, the religious ethic had been that a life was less important than the conditions of it, because a better life lay beyond death. Just as the present social order based on codified government is coming under challenge, this medical ethic based on survival at all costs is now being questioned – not least by the medical profession. It is being questioned particularly both at the beginning of life and at the end. When a live birth is to be prevented, and when a condition is to be treated as terminal are now open questions and will undoubtedly become more so in the next twenty years. The medical profession now has the power of life and death which it has never had before, and which poses major new ethical problems.

Against this background, it is probable that there will be a high concentration of medical research on the two ends of life – paediatrics and geriatrics. In paediatrics, one can do much to form the course of life in terms of health. Geriatrics, on the other hand, should be able to produce the essential treatments for the degeneration inherent in ageing. Thus the aims of health care can be simply stated: a healthy childhood, a productive and satisfying adult life and a comfortable old age. Increasingly, the test of medicine on a life span will be its success of the treatment in each of these periods of life to accomplish the aim set for the following period. It is at least a questionable ethical medical service to mankind to treat at any stage for survival only. The ethical problems involved are much more difficult.

Thus the concept of man adapting, or man surviving, needs to take on a new meaning. The discussion of trends in mortality in the first session of this symposium must pale into the background. We need to turn again towards the religious ethic that the quality of life is more important than its mere prolongation. We need to look carefully at the impact of medical technology not on survival, but on the conditions in which that survival takes place. This, of course, was the theme of David Taylor's paper, and to some extent of Sir John Butterfield's.

The theme running through my own paper has been that it seems likely that medical progress itself may continue to 'create' illness, in the sense that previously tolerable abnormalities will become amenable to treatment and will be judged to be in need of it. Thus man will be adapting to steadily higher levels of avoidance of dis-ease, and medical science will be expected to cater for these higher expectations.

The risk which has been underlined throughout the discussion is that pharmacological progress may in a variety of ways be stifled by excessive bureaucracy. Set against this there is the inevitable growth in public expectations which will grow up alongside an increase in diagnostic competence. Pharmacology can only cater for the consequent increased demands if it is allowed to accelerate rather than to be retarded. There is here a conflict which perhaps we have been trying to make explicit in these discussions. It can be illustrated again in terms of my growth and decay models in Figure 2. The outcome of the conflict, of course, depends on the relative points at which the four 'growth curves' – technological innovation, state bureaucracy, nineteenth century capitalism and mass expectations of independence and wellbeing – reach their apogee and start to go into decline.

Looking specifically at pharmaceuticals and pharmacology, there is no doubt that public and professional expectations will continue their exponential growth well beyond the year 2000. Nineteenth-century capitalism in its traditional form, on the other hand, is already heading towards decline. The era of the economic entrepreneur in the industry is at an end. It is no longer possible to amass high individual fortunes by pharmacological creativity. The question marks, therefore, hang over the curves for technological innovation and for state bureaucracy. How will they affect man's ability to adapt to the environment created by social and technological advances?

If the worst happens – and perhaps this symposium may have done something to avert it – State bureaucracy will continue to flourish while technological innovation stagnates. The outcome is shown in Figure 3. Significantly it shows a 'collision point' between mass expectations and technology somewhere before the year 2000. Although it is dangerous to generalise from a picture intended to relate specifically to pharmaceuticals, it is arguable that if this picture were to apply for technology as a whole, the crossover point between the rise of expectations and the inhibition of technology would signal a revolution against the all-powerful bureaucracy.

The more optimistic view is illustrated in Figure 4. Here it is the bureaucracy which has been held in check, and technology has been allowed to flourish. This was, of course, the picture painted for Britain's future by politicians a few years ago when they spoke of a white-hot technological revolution. Unfortunately, the reality over the past two decades seems to have been nearer to Figure 3 than to Figure 4.

FIGURE 3

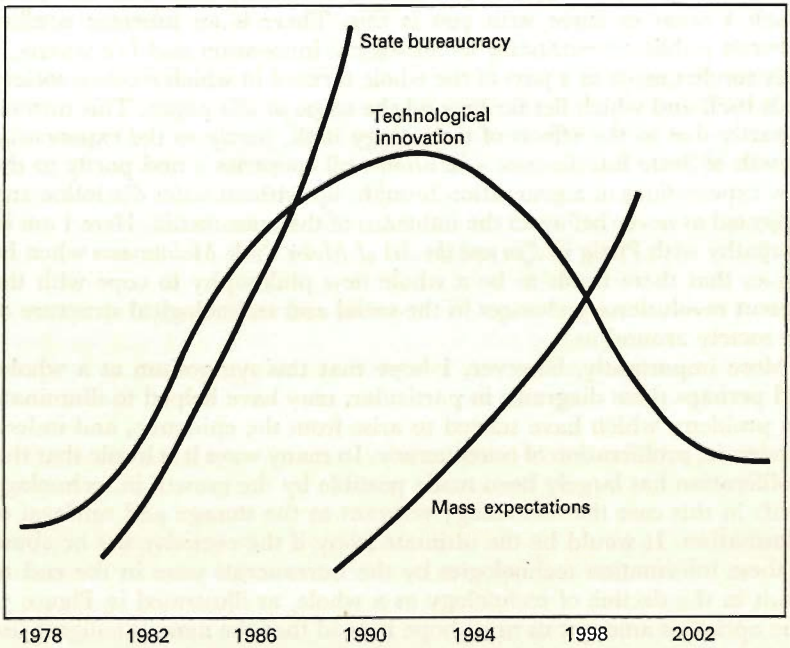
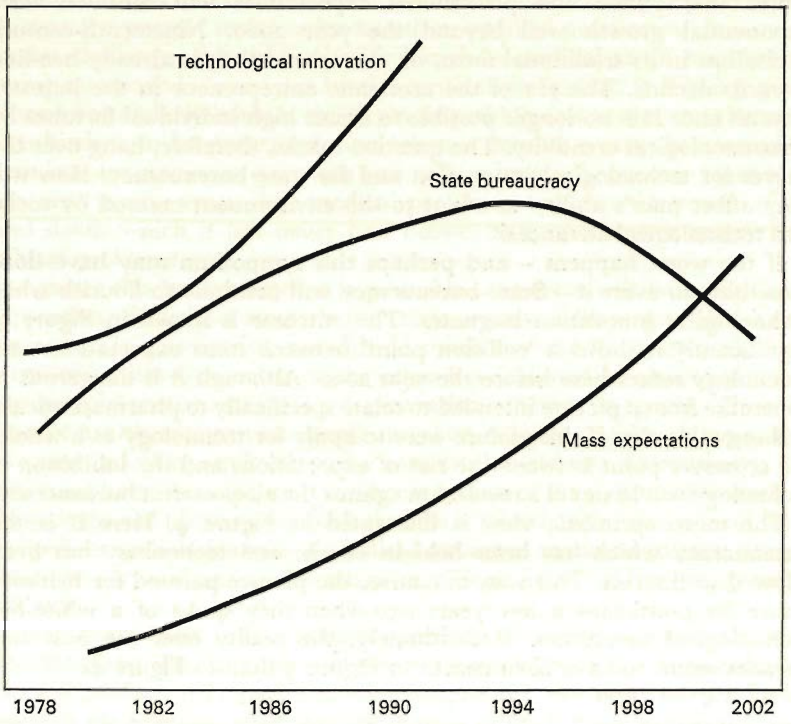


FIGURE 4



Of course, these diagrams are grossly over-simplified. But the point which I want to leave with you is this. There is an inherent conflict between public expectations, technological innovation and bureaucracy. This conflict exists as a part of the whole turmoil in which modern society finds itself and which lies far beyond the scope of this paper. This turmoil is partly due to the effects of technology itself, partly to the exponential growth of State interference – in almost all countries – and partly to the new expectations of a generation brought up without strict discipline and subjected as never before to the influence of the mass media. Here I am in sympathy with Pirsig in *Zen and the Art of Motor Cycle Maintenance* when he argues that there needs to be a whole new philosophy to cope with the present revolutionary changes in the social and technological structure of the society around us.[6]

More importantly, however, I hope that this symposium as a whole, and perhaps these diagrams in particular, may have helped to illuminate the problems which have started to arise from the epidemic, and indeed pandemic, proliferation of bureaucracy. In many ways it is ironic that this proliferation has largely been made possible by the growth in technology itself: in this case the technology relevant to the storage and retrieval of information. It would be the ultimate irony if the excessive use or abuse of these information technologies by the bureaucrats were in the end to result in the decline of technology as a whole, as illustrated in Figure 3. The optimists amongst us must hope instead that the more intelligent use

of the new information technologies both within government and industry may instead result in less need for large-scale bureaucracy: this is the picture in Figure 4. Here bureaucracy has become subservient to the achievements of technology and to the expectations of the people, rather than being their master. This must be the objective for which all of us who believe in the principles of a free democratic society should now be aiming.

I am sure no one would have expected a new philosophy even in the limited context of pharmaceutical innovation to have emerged from a single two-day symposium. However, from the papers which you have heard so far, and the final discussion in which I hope you will now take part, perhaps some light will have been shed on the inherent problems in ensuring a continued steady flow of safe, effective and economical new medicines for all parts of the world.

REFERENCES

1 Burnet M (1962). Natural History of Infectious Diseases (Third edition). Cambridge University Press.
2 Hellman K (1978). Meeting of the Section of Oncology. Royal Society of Medicine, 25 June.
3 Dubos R (1965). Man Adapting. Yale University Press.
4 Pickering G (1974). Creative Malady. George Allen and Unwin.
5 *Lancet* (1978). Psychotherapy for Multiple Sclerosis? 1, 541.
6 Pirsig R (1977). Zen and the Art of Motorcycle Maintenance. Corgi.

Discussants

MR J. MADDOX *(Nuffield Foundation, Britain)*

May I first explain that I am not a Cassandra, but a Pollyanna, so what I have to say echoes Dr Paget much more than what you have said, Mr Chairman.

Since it is my job, I should like to try and draw attention to the things that impressed me in what was said in the earlier session and to ask three questions, one of each of the speakers – you will notice, Mr Chairman, that the last is addressed to you as much as to George Teeling-Smith.

Professor Stähl, as an economist, is probably familiar enough with the experience of talking with people not economists and discovering afterwards that most of them had not listened to what he had said because he had used phrases like 'GDP' and so on, so to encourage him I should like to demonstrate that I did my best to follow what he said.

One of the things that impressed me very much was the argument running through Professor Stähl's paper that in fact one could take the graph which showed how different countries distributed their expenditure on health care among the different sectors – hospitals, physicians and so on – and, as Professor Stähl was saying, extrapolate figures to consider the question what people would be spending in the year 2000, and come to the perhaps cosy conclusion that it will all be all right, people would be spending then more or less what the very rich countries are spending now, and there would still be money left over to buy motor cars and so on.

I should like to ask the question whether we can be so sure that even in this relatively short time between now and the end of the century there will not be a considerable number of changes in the pattern of medical health care activity, and therefore in the pattern of these expenditures. I have in mind the question of psychiatric illness, to which Professor Stähl referred, pointing out that there had been a change in the last few years from hospitalisation to surgical intervention and to the present treatment in the community by means of drugs. But we still know that psychiatric treatment by drugs in the community, although it is better than the treatment of psychiatric patients in hospitals, is still so far from being ideal as to justify in some people's minds the epithet of 'unsatisfactory'. I feel that before the treatment of psychiatric illness is properly dealt with, and before the provision of psychiatric care is properly dealt with, we shall find that a great deal of expenditure will go not on drugs, hospitals or other things of a traditional kind, but rather on social services, which broadly speaking we have not yet had the wit to invent.

I have explained that I rather share Dr Paget's line of argument; indeed, on some matters I would go further than he did. I would not be surprised if the first results of genetic manipulation, for example, are not in clinical trials in three years from now. No doubt there will be vaccines. I am entirely sure that what he has said about the other developments in prospect is true.

There is one thing that he said in passing which I would not like to let

go unchallenged. He asks the question – and he hedged it round with all kinds of qualifications, wondering perhaps whether he was being too cynical – whether the developing countries could afford the prolongation of life on a big scale that could come about by the successful treatment of tropical diseases. Would it be proper for developed countries and the pharmaceutical companies in developed countries to provide means of treating tropical diseases without at the same time being required to provide means of treating conception? He added that perhaps we ought also to pay attention to the social and economic background of the developing countries. I think the dilemma is the other way round. There are many developing countries where the conception rate is too high where the explanation is to be found, partly at least, in the lack of medical services.

If one considers India, for example, where until recently the average number of children per woman was four, that was not an accident. Women in India and their husbands were well aware that when they were children half of their schoolmates would be dead at puberty, the age of fifteen or thereabouts. Therefore, is it surprising that with those recent folk memories, they provide twice as many children as the country really needs? Is it not likely that the most effective way of reducing that birthrate, one essential component in this, is to give them the security in health care and in believing their children and perhaps even they themselves will have a better chance than they would have done twenty years ago?

I think really there is no conflict between the provision of better health care in developing countries and the long-term economic needs of this country.

My last point is addressed to the underlying theme of this conference, the question of regulations. I think that it is not surprising that we have in the past fifteen years a much greater concern in the public at large with safety, not merely of drugs, but of motor cars, of water, of air and of nuclear power stations, together with all kinds of activities in the modern world. George Teeling-Smith was entirely right to draw attention to the increased expectations of the public at large in medicines and pharmaceutical products and the like in the period since the beginning of the 1960s. He might have added that this period has also seen an enormously increased expectation in other kinds of goods and commodities – prosperity, wealth, possession of a colour television set, the right of a person who goes to university and gets a degree to have a white collar job, even if society does not need more people like him, and all those things which have happened in the past seventeen years. I think the question that faces people, not merely those in the pharmaceutical industry but all of us, is how in fact to bring about a much more realistic appreciation of what is feasible.

You, Mr Chairman – and this is why the question is addressed to you – said that perhaps we have to rely on academics and others to help to bring this about. I must tell you some of my best friends are academics, nevertheless I would not leave it to them, because it is a much more basic issue. First of all it is a political issue that affects the way in which wage demands in this country are to be balanced against the country's national income; the way in which our national expectation of better services of all kinds – not just of medicine – is to be restrained by knowledge of what is

feasible. It seems to me that in that broad sense it is a political argument that all developed countries need to have.

So far as the pharmaceutical industry is concerned, I should have thought that the physician must play an especially important part in arriving at the necessary trade-off between the freedom from bad luck, which people look for in their expectation that no drug will have any side effect at all, and the benefits of taking such a drug. Therefore I would very much like to see what George Teeling-Smith referred to in his talk come about – a much more direct understanding of what mortality represents for the people of countries like ours. I think, for example, there will have to be a much more realistic appreciation by people in their fifties or sixties that there may be a trade-off between mental alertness in their seventies and the use of drugs that reduce hypertension, and which might then avoid a stroke.

I wonder how you, Mr Chairman, on reflection, would like to see this campaign done – not entirely, I hope, by the academics.

MR B. G. JAMES *(Merck Sharp & Dohme, United States)*

I found Dr Paget's paper admirable. I would subscribe to much of what he presented here today, and I agree with his optimism, even at the considerable risk of being wrong. I think that anybody who forecasts the future must live with the very real probability that his or her projections will not materialise in the form or time-frame originally predicted. Any predictions that do come to pass might mean that the forecaster has been cast at some time as a heretic, possibly for thinking the unthinkable. Let us look back a few years to Ernst Schumacher, the proponent of 'Small is Beautiful'. He worked once as Economic Advisor to the National Coal Board in Britain and came out with the prediction in 1961 of an oil crisis within twenty years at a time when we were awash in oil. That may have led to his early retirement!

I have two major concerns with any technological forecast concerning the pharmaceutical industry. One is that you cannot evaluate drug technology without evaluating other environments within which the industry will operate and which will heavily influence the discovery, production and introduction of all new drugs. As an industry we tend frequently to forget that drugs are just one part of health care delivery. Changes in technology, usage patterns and of perceptions of value in other modes of health care delivery will impact significantly on the therapeutic type and overall demand for drugs in the future.

Secondly there is a tendency to limit technological forecasting to defining product possibilities for existing problems. Presumably, the future will be no different from the past and we shall continue to discover additional medical problems when we lift more stones. In the last decade we have had some bizarre afflictions, some of which have been mentioned today – Legionnaire's disease, Green Monkey disease and Lassa fever; these are the sorts of things that we did not know existed ten years ago. There is also the possibility of the re-emergence of new and resistant strains of infectious diseases which we thought were very much under control. I would point

out that yesterday there was the first death from smallpox in the United Kingdom for five years. Overall, I do not feel that technological advance will be such a problem, provided that a balance can be reached which successfully meets the multiple demands of social desirability, medical utility, political acceptability, economic benefit and something very dear to my heart, adequate commercial return.

In commenting on George's paper, I have certain problems with it. He presented a somewhat alarming future scenario, which I suppose could be called 'Close encounters of a bureaucratic kind'. George is right, there is an increasing level of bureaucracy, but that is not applicable only to the pharmaceutical industry. It runs parallel with the increasing government intervention in the economy, and in the move towards centralist government. A recent OECD report indicated that by the mid-1970s, public sector expenditure by governments in most of the developed nations, excluding nationalised industries, accounted for over 40 per cent of their national gross domestic product. Government intervention on that scale requires an army of bureaucrats to administer. I feel that George in concentrating on the bureaucracy issue has clouded the fundamental political issues facing medicine.

I should like to mention two points referred to by Professor Stähl, and also one which was followed in several discussions. The first is the cost of health care. Social security programmes are significantly under-financed, and with the rocky economic state of the world today have become an unsustainable burden. We have a situation which is going to get worse. We have low fertility rates and we have an inactive population which is growing at a faster rate than the working population. When one considers it in a different light, it is highly unlikely that the active working population, already chafing under today's tax burden, will be able or willing – and I think willing is the word – to assume the heavier tax burden projected for the future. We have already had a tax revolt in the United States in California, and I think that that may well occur in other countries.

It should be noted, particularly in Europe, that in the past at any time national governments wanted to find money, they took it out of defence. Defence expenditure has reached such a low level now that governments will have to look somewhere else, and social security and health care seem to be the obvious, open-ended opportunity from which to find money.

Probably what is needed is a complete re-evaluation of society's and government's concept of health care delivery. The pharmaceutical industry is in a delicate position, being largely the only private sector in a public health care delivery market in most of the countries with which we are all familiar. Whipping the pharmaceutical industry at regular intervals on prices, profits, promotion, patents and other assorted assumed sins is an easy way for governments to avoid making sensible health care policy decisions and facing up to their responsibilities to society.

I will not go into government intervention in the regulatory process, because I think it has been covered adequately by Brian Cromie but one wonders whether society or government is the engine which is the driving force behind regulatory control. One gets the feeling frequently that society's needs are being prejudged by government and that there is not a full dialogue of both risks and benefits of drug therapy between government

and society. There is not only a need for a sense of perspective, which has been mentioned before, but a real dialogue with society, if government is really serious about considering the needs and desires of society.

I was going to say at this point that no-risk drugs are like no-pregnancy motherhood, but what with test-tube babies, I do not think that that statement is going to stand up in the future.

I should like to suggest that the future of medicine, the pharmaceutical industry and much of society's health in the next 22 years will depend largely on the early recognition by society, government and industry that they have mutually compatible goals – efficient, ample and equitable delivery of health care to all.

MR S. M. PERETZ *(Deputy Executive Vice-President, IFPMA, Switzerland)*

I am going to exercise my prerogative as the last discussant in making my own comments rather more wide ranging than those offered by the previous speakers.

I am neither a pessimist nor an optimist; I am a realist. Could anyone who happens to live in the United Kingdom have believed after Sainsbury that they would have heard a socialist Minister of Health get up before a meeting, as he did last night, and give a panegyric about the pharmaceutical industry? I do not think that any of us could have forecast that that would be the outcome of the post-Sainsbury period. I think the only way of explaining the comments that Roland Moyle made last night about the industry at large is that he has been educated to understand that the pharmaceutical industry plays a key part in the United Kingdom's economy. It is one of the few industries that is still showing growth.

We have heard a great deal in the last two days about the fears of the industry. I should like briefly to highlight some of those fears and talk about them and about the future as far as these things are concerned. I feel there is a danger that we in the industry may be accused of crying wolf perhaps once too often. After all, we are alive and well; the industry is growing, and although there may have been a drop in the number of new products arriving on the market, no one could deny, for instance, that when a genuinely major new product does arrive on the market, as Tagamet did the other day, it still brings rich rewards for its innovator. Who is to say that another company tomorrow is not going to continue that process? Max Tiefenbacher – and I have to be careful here because in my new job as Executive Vice-President of the IFPMA I am responding to him as President – made the comment that because the industry put down blue chips it wanted blue chips back. Perhaps this comment has given some pople the wrong idea that we are in a gambling industry. We are not in a gambling industry, we are in a risk-taking industry. We have always accepted the fact that we are in a risk-taking industry. The going rate to enter the game is certainly much more expensive than it used to be. The necessity of spending eight to ten years before getting a product on the market and of going through procedures that may cost anything between US$15 to US$40 million means that to enter the game one has to

have money in one's pocket, but it is still possible to make a success of what one is doing.

I think one thing that we have shown the British Government is that because it is a risk-taking industry this is an industry that is well suited to private enterprise, and is very ill-suited to nationalised industry.

What are we afraid of? We are afraid of government intervention on price control, which by its nature is almost inevitably an arbitrary process. Even price controls that work today, will certainly not work tomorrow. They are going to put a sort of strait-jacket around our possibilities for the future. In some countries, of course, they do not exist, but all the signs are that this is an encroaching mechanism by government everywhere, to which we have to pay attention.

We are worried about the loosening of patent control. I think I heard somebody say that there was a strong possibility that the United States patent life of seventeen years was going to get shorter. We have managed to convince our government in the United Kingdom that not only should patent life be twenty years, but it should remove this terrible business of compulsory licensing. I hope that the forces of reason will prevail and that we can strengthen, not weaken, the patent system. I think it is necessary to fight for it, and very good arguments can and must be used.

We are worried in the industry about regulatory controls, not just because of this obsession with safety about which we have heard so much, but because so many of these regulatory controls are self-defeating or alternatively that they are duplicating efforts in other parts of the world, so that the whole grinding mechanism has to be repeated in many countries at the most astonishing cost and frankly with very little benefit in the long run. We are concerned about those sort of things. I believe that we have something to be concerned about and that there is every reason why we should voice that concern. I think we should debate it with the medical profession. I think we should debate it with the public.

It is the potentially sick people who ought to be aware that the only real hope for the future for those who today suffer from multiple sclerosis for which there is no treatment or cure is that this industry is going to come up with something that is going to help them in the future. We have to bring this argument to the public. We have to explain that research and development is not something that can be exercised on a yearly basis. There is a long-term process. I should like to have heard in the last two days from people in the audience who I know come from the research departments of the companies and who know better than I do that to get a research team together, working on a project, involves at least a ten-year span, and that the research people themselves require the confidence that they are going to be in employment throughout their time; the money is going to be there to pay their wages and salaries; that in the long run, if they come up with a product, there is every likelihood that it will be marketed.

With regard to all of these problems for the future, as I said I am an optimistic realist. I believe that there is some ground for optimism and that we have the trump card of commonsense; that if the public knew about the sort of things I have been talking about it would appreciate that ours is an industry to encourage and not to stifle.

I believe that in the year 2000 we shall have an active and progressive pharmaceutical industry. I also believe that more innovations are coming forward not fewer. It is only that they need to be much more carefully selected when one considers how much money has to be put behind them.

GENERAL DISCUSSION – SESSION IV

The discussion period following the papers presented to the final session of the symposium provided an opportunity for Professor Louis Lasagna to summarise and comment on some of the major themes which had emerged during the meeting.

The first problem he drew attention to was the deficiency of a suitable means of measuring various aspects of the quality of medical care. Mortality statistics, as Professor A. L. Cochrane had clearly demonstrated, are of only limited use in this context. Furthermore, Lasagna emphasised that discrete measurements frequently reflect the effects of more than one or two variables. For example, the benefits of medicines may appear different in circumstances of ordinary medical practice and drug selection of variable quality to the benefits which had been indicated by extensive pre-marketing tests and trials for the same medicines.

With regard to problems of an economic nature, Lasagna made two general observations. Firstly, quality and benefits are not necessarily positively correlated with size and money. Secondly, he expressed concern at the tendency of both the authorities and the general public to concentrate their attention on short-term problems – especially the means of reducing the drug bill. In this respect, he noted the failure, in the United States at least, to examine the short and long-term benefits and harms of generic substitution.

Cochrane predicted an optimistic future for the health service because of the increasingly important role he foresaw for evaluative techniques in facilitating sensible spending decisions – notably in the primary care services. Professor I. Stähl suggested that the use of evaluation in hypothetical models may also generate useful information in attempts to solve the problems of financing health care provision. He proposed, for example, that it would be instructive to examine patient behaviour in situations where the latter is financially able to make choices between surgical and chemotherapeutic alternatives. Stähl suggested that the potential value of models such as these tends to be underestimated.

Turning to the problems of the third world, Lasagna considered that the pharmaceutical industry had been given insufficient credit for its achievements in this area. However, he believed that there was still much non-interest in many segments of the industry in moving into areas that are both very expensive and unlikely to be successful. In devising appropriate strategies for obtaining their drug requirements Lasagna recommended that some emerging nations of the world ought to rely on imports and should abandon desires to establish their own innovative pharmaceutical industries until economic progress has reached an appropriate stage of advancement.

The problem in this instance is one of reconciling national pride with

reality. More generally, Lasagna viewed the whole problem of unrealistic expectations as a serious obstacle to progress. There is a clear need, for example, to educate the public about what is feasible and realistic and this can only be achieved through a collaborative effort involving academics, the industry itself, the medical profession and other interested bodies. A similarly realistic approach also leads to the conclusion that medicines are unlikely to cut national health costs. Although Stähl had earlier pointed out that they provide one of the least expensive means of care, the price to be paid for innovation is increasing and greater numbers of people are now surviving to old age and requiring medical care.

In spite of the pessimism stemming from the problems raised during the symposium Lasagna concluded on an optimistic note. Prognostication is of course a hazardous business. But history has shown us that whilst some developments have been predictable and deliberately pursued others have occurred quite unexpectedly (although soon after their appearance, surprise is frequently expressed at the failure to have anticipated such events). In view of this Lasagna predicted that the year 2000 will hold some pleasant surprises which are far beyond our current expectations.

Session Chairmen, Principal Speakers and Discussants

SIR DOUGLAS BLACK
President of the Royal College of Physicians;
Formerly: Chief Scientist, Department of Health and Social Security;
Professor of Medicine, Manchester University.

DR M L BURSTALL
Department of Chemistry, University of Surrey.

PROFESSOR SIR JOHN BUTTERFIELD
Chairman, UK Medicines Commission;
Regius Professor of Physic, Cambridge University;
Formerly: Vice-Chancellor, Nottingham University;
Professor of Medicine, Guy's Hospital.

PROFESSOR A L COCHRANE
Formerly: Director, Medical Research Council Epidemiology Unit;
Professor of Tuberculosis and Chest Diseases, Welsh National School of Medicine;
Author of 'Effectiveness and Efficiency; Random Reflections on the National Health Service', 1972.

DR BRIAN CROMIE
Member, UK Medicines Commission;
Vice-President, Association of the British Pharmaceutical Industry;
Chief Executive, Hoechst Pharmaceuticals, UK.

DR GORDON FRYERS
Consultant Director of Medical Affairs, Proprietary Association of Great Britain;
Director of Strategic Affairs, Reckitt and Colman.

PROFESSOR HENRY GRABOWSKI
Professor of Economics, Duke University;
Author of 'Drug Regulation and Innovation', 1976.

BARRIE JAMES
Merck Sharp and Dohme, United States;
Author of 'The Future of the Multinational Pharmaceutical Industry to 1990'.

PROFESSOR ERICH KAUFER
Professor of Economics, Innsbruck University;
Author of 'Die Oekonomik der pharmazeutischen Industrie', 1976.

DR SANJAYA LALL
Institute of Economics and Statistics, Oxford University;
Author of 'Major Issues in Transfer to Developing Countries; a case study of the pharmaceutical industry', 1975.

PROFESSOR LOUIS LASAGNA
Professor of Pharmacology and Toxicology, University of Rochester;
Joint Author of 'Regulation and Drug Development', 1975.

PROFESSOR THOMAS McKEOWN
Formerly: Professor of Social Medicine and Pro Vice-Chancellor, Birmingham University;
Author of 'The Role of Medicine; Dream, Mirage or Nemesis?' 1976.

JOHN MADDOX
Director, Nuffield Foundation;
Formerly: Editor, 'Nature'.

A J MERIFIELD
Under Secretary, Department of Health and Social Security.

DR MARK NOVITCH
Food and Drug Administration, US Department of Health Education and Welfare;
Formerly; Assistant Staff Director, Task Force on Prescription Drugs.

DR EDWARD PAGET
Member, UK Medicines Commission;
Director, Inveresk Research International.

DR JOHN PARKER
Department of Economics, Otago University;
Author of 'The Economics of Innovation', 1974.

MICHAEL PERETZ
Deputy Executive Vice-President, International Federation of Pharmaceutical Manufacturers' Associations;
Past President, Association of the British Pharmaceutical Industry.

DR DUNCAN REEKIE
Department of Business Studies, Edinburgh University;
Author of 'The Economics of the Pharmaceutical Industry', 1975.

PROFESSOR DAVID SCHWARTZMAN
Professor of Economics, New School for Social Research, New York;
Author of 'Innovation in the Pharmaceutical Industry', 1976.

PROFESSOR INGEMAR STÄHL
Professor of Economics, Lund University.

SIR MICHAEL SWANN, FRS
Chairman, British Broadcasting Corporation;
Formerly: Vice-Chancellor, University of Edinburgh;
Dean of the Faculty of Science, Edinburgh University.

DAVID TAYLOR
Deputy Director, Office of Health Economics.

GEORGE TEELING-SMITH
Director, Office of Health Economics.

MAX TIEFENBACHER
President of the International Federation of Pharmaceutical Manufacturers' Associations;
Director, Hoechst, Germany.

LORD VAIZEY
Head of the School of Social Sciences, Brunel University;
Author of numerous books on economics.

PROFESSOR WILLIAM WARDELL
Associate Professor of Pharmacology and Toxicology, University of Rochester, School of Medicine and Dentistry;
Director, Centre for the Study of Drug Development;
Joint Author of 'Regulation and Drug Development', 1975.

G J WILKINS
Past President, Association of the British Pharmaceutical Industry;
Chairman, Beecham Group Ltd.

Index