PHARMACEUTICAL INNOVATION:

recent trends, future prospects

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Cover illustration, showing Pasteur in his laboratory, by courtesy of the Mary Evans Picture Library

This paper was researched and written by **Nicholas Wells**

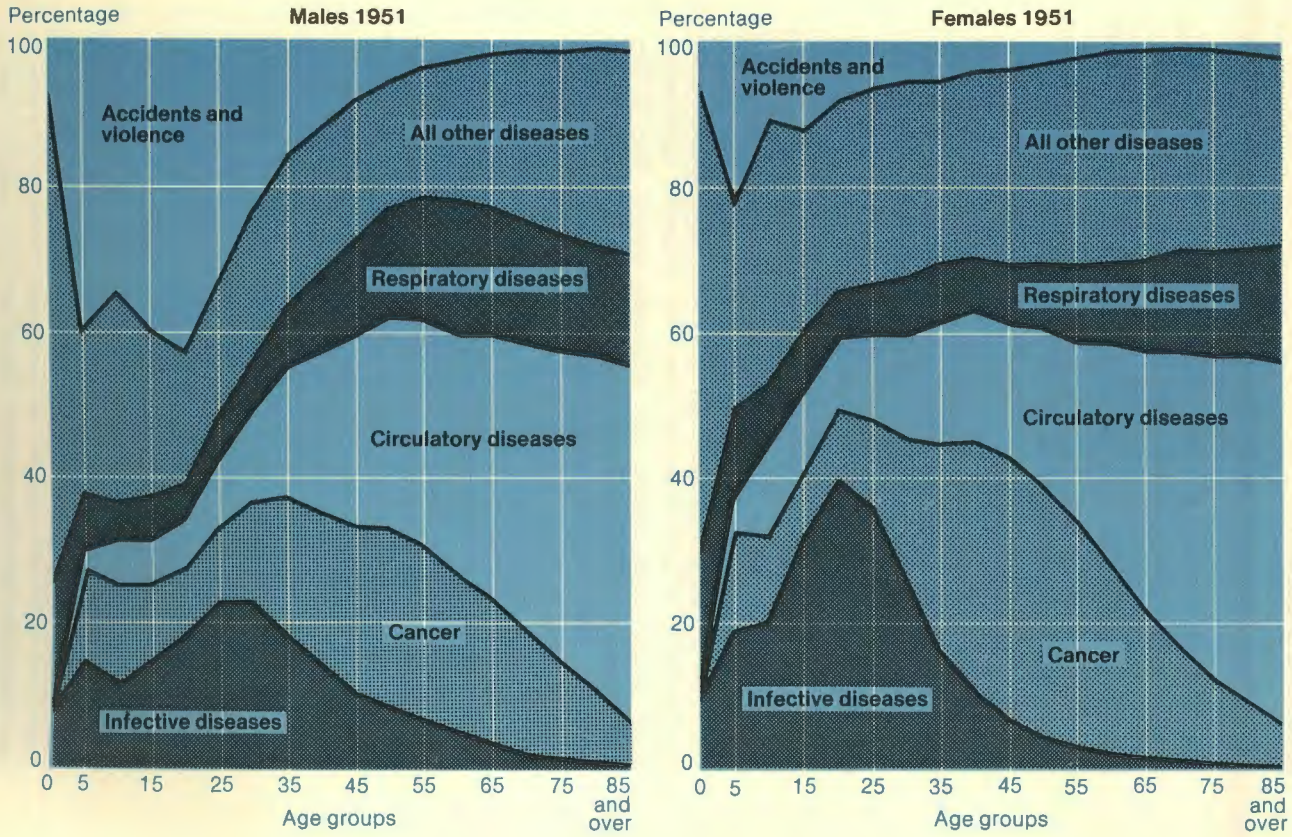
Introduction

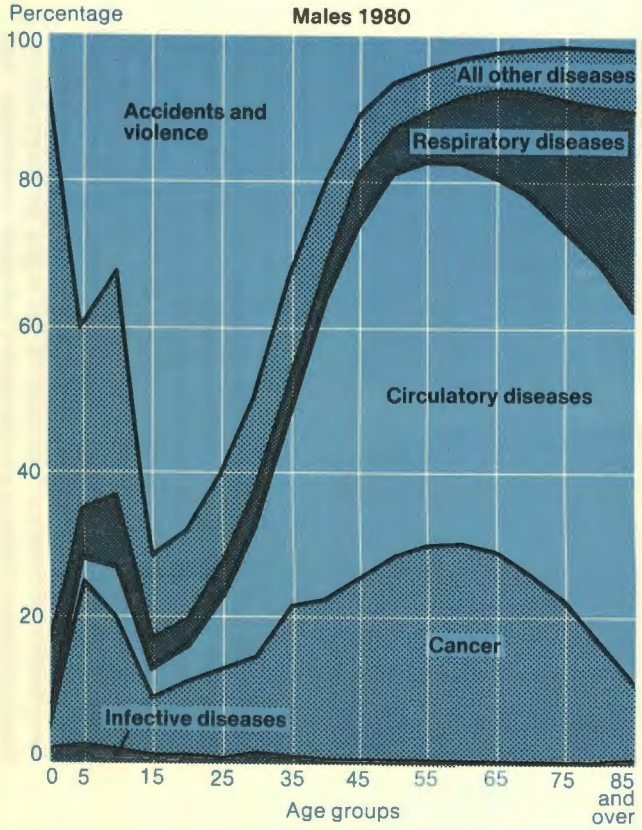
Therapeutic progress in recent decades has made a major contribution to reductions in mortality and has extended effective control to the symptoms of many chronic diseases. Thus developments in chemotherapy and immunisation have combined with economic, social and environmental improvement to bring about the restructuring of mortality profiles illustrated in Figure 1. The principal change has been of course the dramatic reduction in the number of deaths attributable to infectious disease: between 1951 and 1981 the crude death rate per million population for infective and parasitic diseases fell from 408 to 42, generating a current annual saving of more than 18,000 lives.

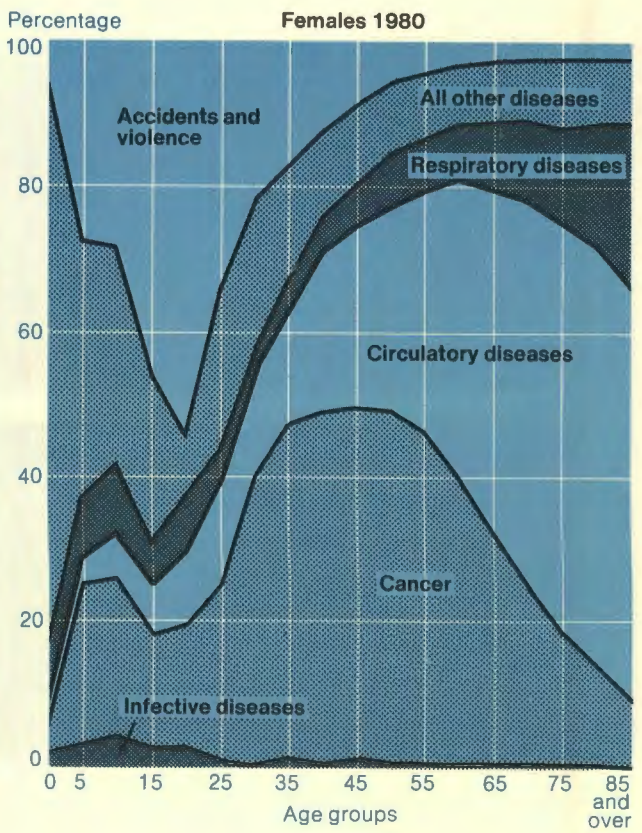
Within this broad disease grouping the most dramatic improvement has been shown by respiratory tuberculosis. Here the mortality rate has declined by 97 per cent over the same period so that in 1981 there were just 433 deaths from this cause compared with the 13,650 that might have been expected in the absence of any change in the death rate. The impact of anti-infective chemotherapy and effective vaccines has not, however, been restricted to tuberculosis alone: notifications data (Table 1) and mortality statistics (Table 2) indicate that there have also been major reductions in the incidence of and mortality from, for example, diphtheria, acute poliomyelitis, syphilis and whooping cough. One of the consequences of these and other improvements has been a halving of the child mortality rate over the 30 year period to 1981 (when it stood at 31 per 100,000 aged 1–14 years) and thereby the addition of a further three years to average life expectancies at one year of age (Figure 2).

The benefits of chemotherapeutic progress have also been directly manifest in diseases other than those resulting from infectious causes. The development, for example, of prophylactic therapy for asthma as well as the selective beta agonist drugs which rapidly effect control of attacks of breathlessness have greatly improved the quality of life and provided psychological assurance for many asthmatics. Similarly, the evolution of non-steroidal, anti-inflammatory drugs has generated considerable gains for many of the hundreds of thousands of individuals suffering from diseases of the joints and organs of movement by promoting greater mobility and pain control. In both these instances, however, the patient benefits principally assume the form of enhanced well being and social functioning and as such are not as readily measurable as those associated with advances leading to reductions in mortality or hospital admissions. Indeed, the last 20 years have witnessed a period of 'therapeutic transition' in which new medicines have increasingly fallen into this category, that is they have had a greater impact on the quality of life than on its

Figure 1 *Selected causes of death by age and sex, Britain 1951 and 1980.*







Note Data for 1980 relate to the United Kingdom.
Source *Social Trends*, Nos 11 and 13.

Table 1 *Notifications of selected infectious diseases, England and Wales, 1951–81.*

	Whooping Cough	*Scarlet Fever*	*Diphtheria*	*Acute Poliomyelitis*		*Respiratory Tuberculosis*
				Paralytic	*Non-paralytic*	
1951	169,300	48,700	826[a]	1,527	1,082	50,400[a]
1956	92,400	33,100	57[a]	1,715	1,482	37,500[a]
1961	24,500	20,000	51[a]	731[a]	178[a]	22,200[a]
1966	19,400	21,200	20[a]	21[a]	4[a]	14,300[a]
1971	16,800	12,500	17[b]	7[b]	3[b]	10,800[b]
1976	3,900	9,700	2[b]	12[b]	3[b]	9,200[b]
1981	19,400	7,100	5[bc]	2[bc]	1[bc]	7,800[bc]

a) Figures are for GB.
b) Figures are for UK.
c) 1980 Data.

Source *Social Trends*, Nos 12 and 13.

Table 2 *Number of deaths from selected infectious diseases in England and Wales in1951 and 1981.*

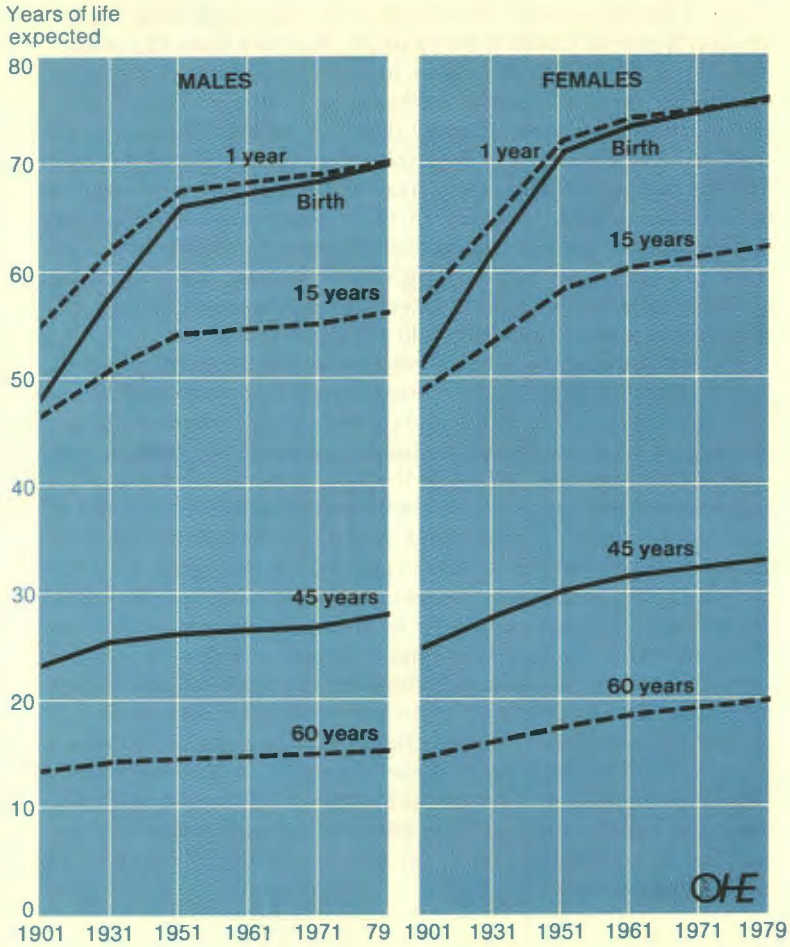
	1951	*1981*
Tuberculosis of respiratory system	12,031	433
Syphilis	1,771	56
Scarlet fever and streptococcal sore throat	66	3
Diphtheria	33	—
Whooping cough	456	5
Meningococcal infections	298	85
Acute poliomyelitis	191	—
Measles	317	15
Rheumatic fever	378	2
Chronic rheumatic heart disease	10,853	3,117
Sepsis of pregnancy, childbirth or puerperium and other maternal causes including abortion	566	65

Source Annual Abstract of Statistics.

duration. In this context mention might also be made therefore of beta blockers for angina and hypertension, the anxiolytics and antidepressants for psychiatric morbidity, preparations for common skin complaints and chemotherapy for gout.

Concomitantly, pharmacological advance has played what might be viewed as a more indirect role in facilitating therapeutic progress. Thus the development and refinement of effective local and general anaesthetic agents, muscle relaxants and antibiotics have facilitated a radical extension of the scope for surgical intervention, greatly enhanced the safety of such procedures and played a part in promoting economical short stay surgery. In addi-

Figure 2 *Expectation of life from birth and other selected ages, United Kingdom, 1901–1979.*



Source *Social Trends*, No 13.

tion, the risks of operations requiring cardiopulmonary bypass have been reduced by the availability of agents inhibiting extra corporeal blood platelet aggregation and the development of immunosuppressant drugs has laid the foundations for a new era in which transplantation has become a feasible approach to diseased or malfunctioning organs.

The health, social and economic benefits (Table 3) attributable to the widening scope for therapeutic intervention coupled with the significant levels of inadequately treated morbidity still remaining in the community have provided a powerful incentive

to continued investigation of the causes of, and potential solutions to, disease. As a consequence research expenditures have maintained a steady pattern of increase over time. Spending by the Medical Research Council, for example, has risen from £25 million in 1971/72 to over £106 million in 1981/82 (Figure 3). Financial support for medical research forthcoming from the nation's medical charities was valued at more than £70 million in 1982 having risen from approximately £25 million in 1976 when aggregated data for this sector first became available. Expenditure growth has been most marked, however, in the research and development undertaken by the pharmaceutical industry: spending increased from £29 million in 1970 to £419 million in 1982. Even after the effects of inflation have been taken into account this increase still represented a more than threefold growth in real terms.

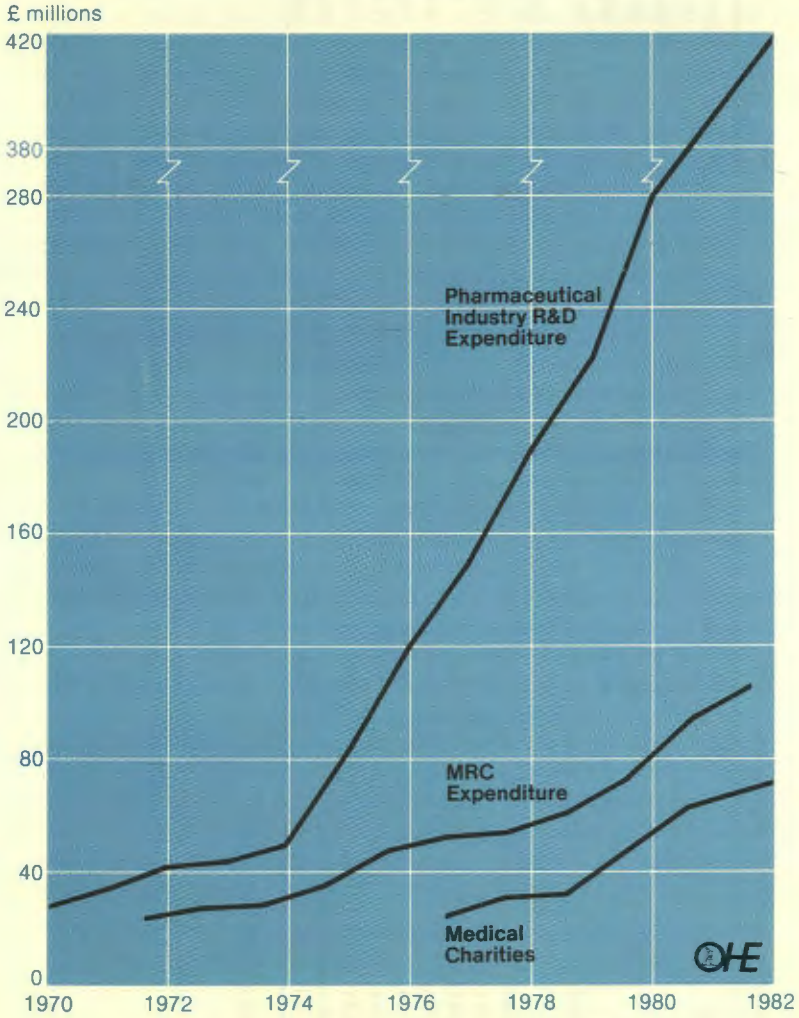
Yet sustained growth in research and development expenditures to the current level of almost £600 million per annum has not been accompanied by any corresponding acceleration in the number of new medicines becoming available for patient use. Indeed, the opposite has been the case: new market entries – including reformulations, new combinations, additional modes of presentation and new chemical entities – numbered approximately 300 per annum at the beginning of the 1960s, but had declined to less than 100 by the end of the following decade. Focusing on new chemical entities (NCEs), the most innovative of these introductions, a similar pattern has emerged: a review by Steward and Wibberley (1980) indicates that over the same period of time marketing rates have halved to the present level of around 20 NCEs per annum (Figure 4). This paper therefore sets as one of its central objectives the exploration of these seemingly paradoxical trends. From this analysis it is hoped to identify the essential preconditions that must be fulfilled if the potential for therapeutic advance outlined in another section of the paper is to be fully realised in the coming decades.

Table 3 *Estimated savings in hospital bed days in England and Wales.*

	1957			1978			*Saving in 1978 as result of fall in total bed days*
Disease	*Patients*	*Bed days*	*Average bed days per patient*	*Patients*	*Bed days*	*Average bed days per patient*	
							£ millions
Asthma	20,935	388,899	18.6	41,380	307,956	7.4	3.6
Epilepsy	11,041	498,553	45.2	24,150	268,530	11.1	10.1
Glaucoma	9,687	150,609	15.5	11,770	123,361	10.5	1.2
Hypertensive Disease	31,012	1,198,113	38.6	20,710	280,838	13.6	40.5
Pneumonia	73,359	1,921,036	26.2	59,110	1,088,305	18.4	36.7
Bronchitis	47,739	1,273,082	26.7	41,560	917,476	22.1	15.7
Skin Diseases	60,195	1,140,773	19.0	72,170	907,738	12.6	10.3
Mental illness	Beds occupied daily = 143,800 (1959)			Beds occupied daily = 77,702 (1979)			354.0
Tuberculosis	67,200 (1955)	10,080,000	150.0	6,170 (1979)	230,758	37.4	300.0

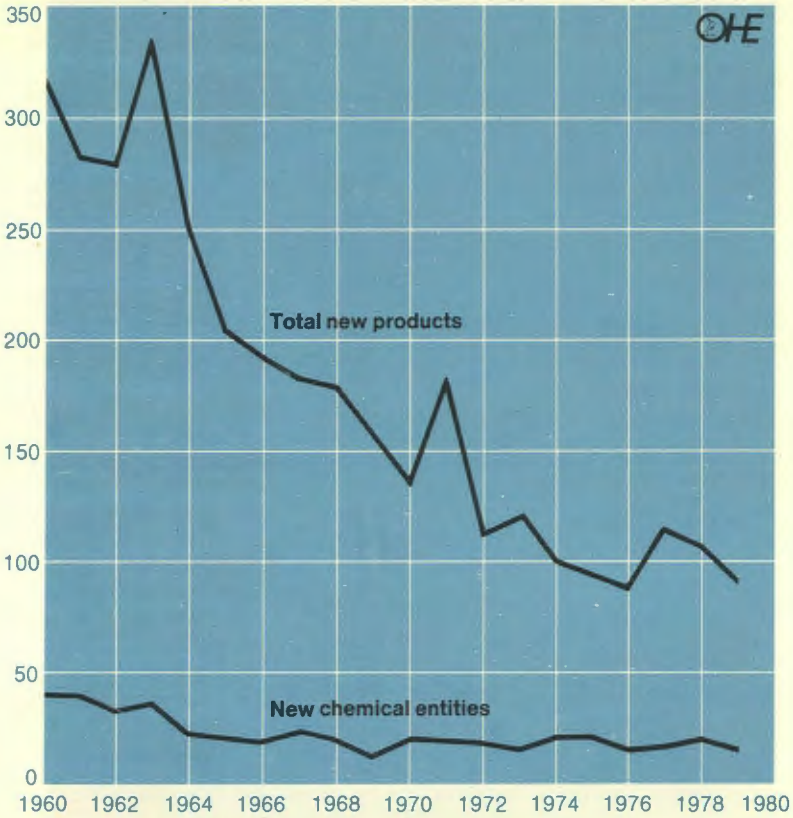
Source Hospital Inpatient Enquiry and OHE Estimates.

Figure 3 *Expenditure on* R *and* D *by the pharmaceutical industry, Medical Research Council and the medical charities, £ millions.*



Source MRC annual report, Handbook of the Association of Medical Research Charities, ABPI annual report.

Figure 4 *Pharmaceutical products introduced into the UK 1960–1979.*

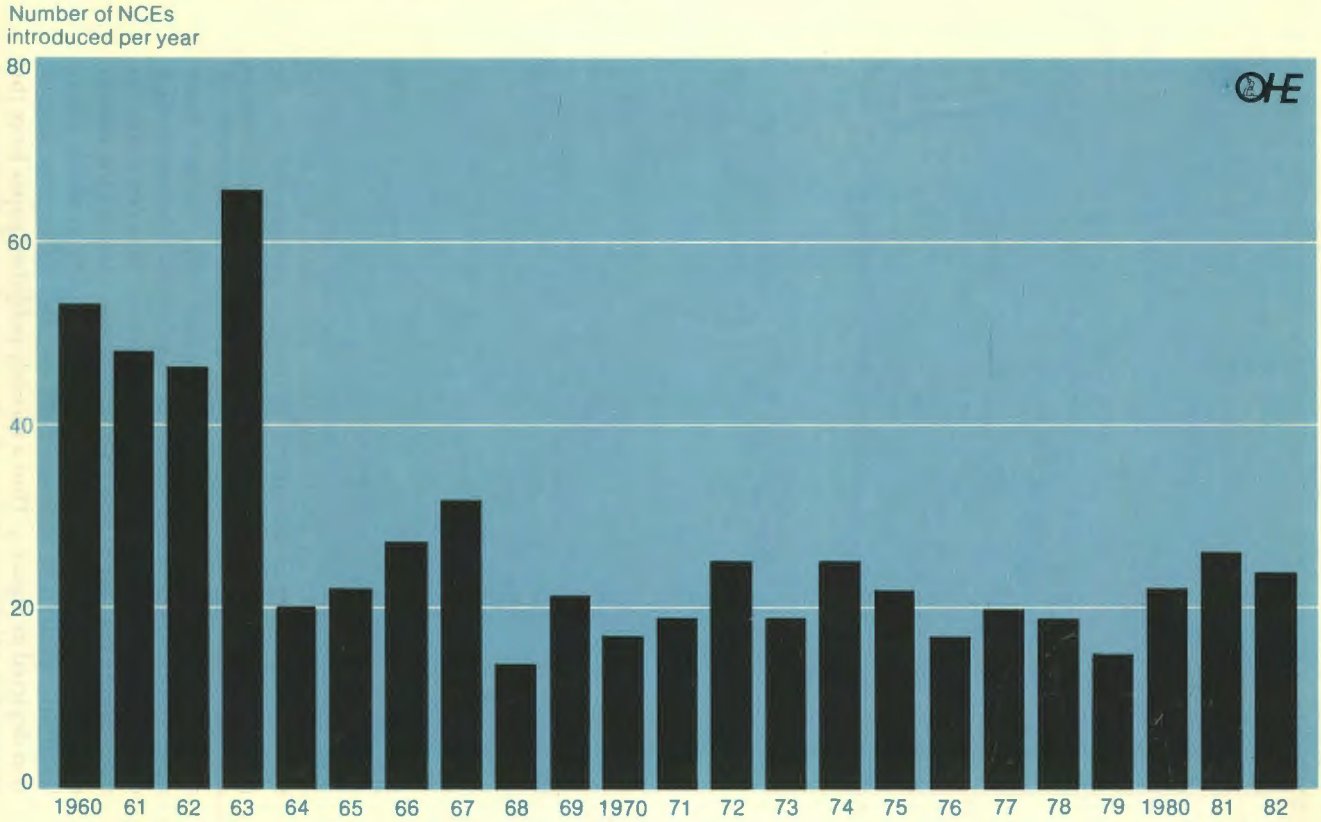


Source Steward and Wibberley 1980.

Trends in innovation

Analyses of trends in pharmaceutical innovation are inevitably beset by a number of difficulties. In the first instance there is the problem of defining a new chemical entity. Surveys published to date have differed with regard to the inclusion or otherwise of, *inter alia*, drugs restricted to use in hospitals only, vaccines, semi-novel combinations and a variety of 'borderline' substances. As a consequence there is some degree of variation between studies in the reported number of new chemical entities reaching the market each year. Nevertheless, the data series currently available corroborate the pattern of innovative decline and subsequent stagnation depicted in Figure 4. Thus a recently published paper from the Centre for Medicines Research (Ravenscroft and Walker 1983)

Figure 5 *Number of NCEs introduced into the* UK *market, 1960–82.*



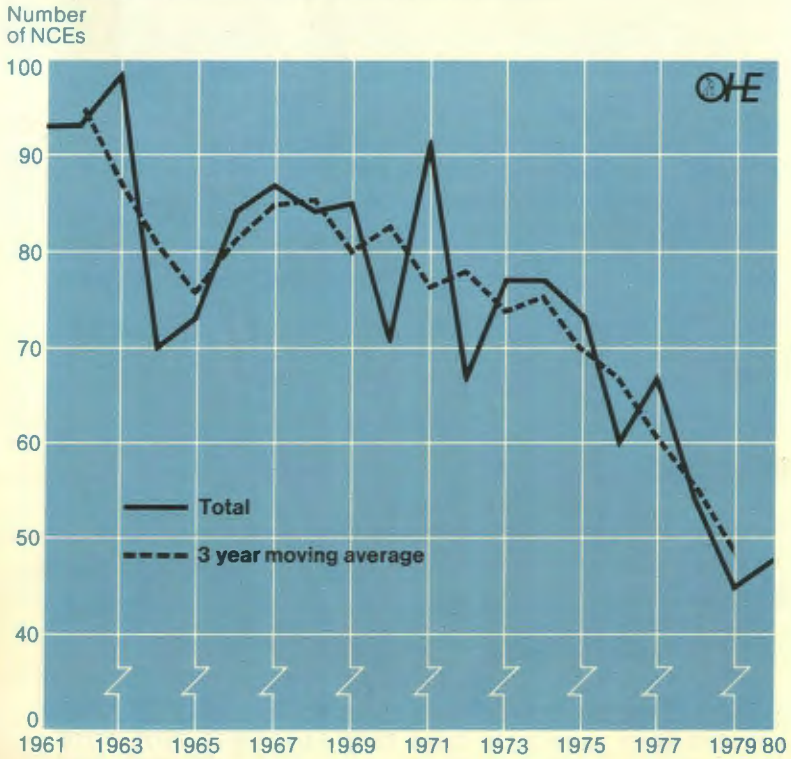
Source Ravenscroft and Walker 1983.

showed that in the period 1960–63 an average of over 50 NCEs were marketed in the UK each year. This was followed initially by a sharp decline to around 25 products per annum between 1964 and 1967 and subsequently by a further fall to an annual level of 20 NCEs which has persisted to the present day (Figure 5). A similar pattern may also be observed on a worldwide scale: Figure 6 is based on data collected by Reis-Arndt (1982) and shows that the number of new chemical entities introduced for the first time in one country or another has fallen from 93 in 1961 to 48 in 1980.

Second there is a protracted time lag between the discovery of a potentially useful chemical substance and its transformation into a therapeutically active prescribable medicine. Consequently investigations of the factors underlying trends in pharmaceutical innovation need to focus attention on the earliest and subsequent stages in any given product's lifecycle and not solely on its date of launch. Unfortunately, the information necessary to satisfy this requirement is rarely available.

One final obstacle derives from the fact that the modern

Figure 6 *Worldwide introductions of NCEs 1961–1980.*

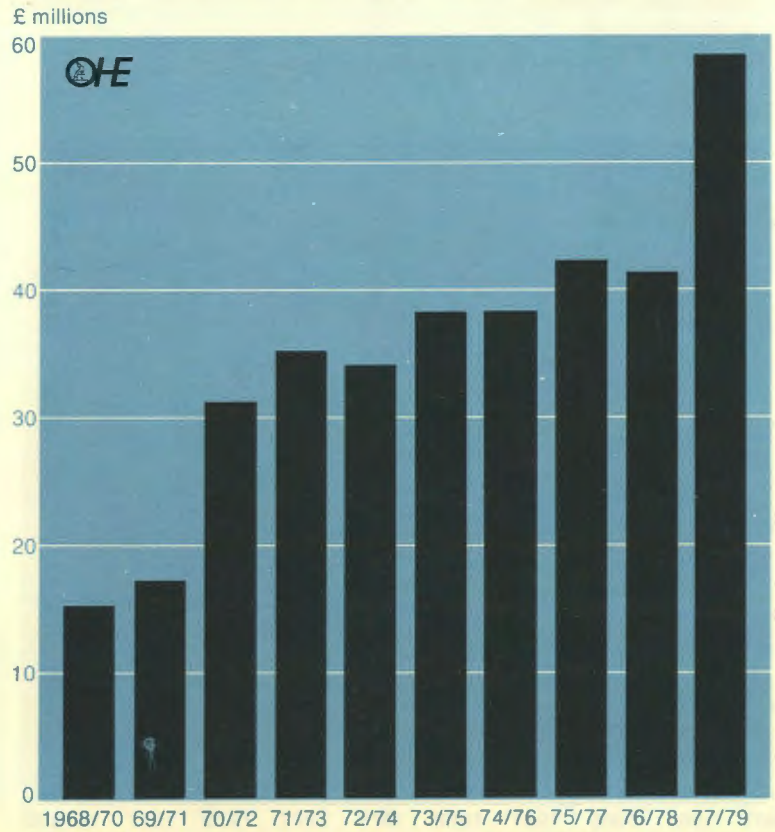


Source Reis-Arndt 1982.

research based pharmaceutical industry is comprised of companies possessing diverse national backgrounds. In the United Kingdom in 1980, for example, of the 85 major manufacturers (which together accounted for 95 per cent of sales to the NHS) 36 were American-owned, 33 were of European parental origin and only 16 companies were indigenous to the home market. The clear implication of this pluralistic industry structure is that among the factors influencing the introduction of new products onto the British market will be those which have a bearing on the innovative climate in other countries.

In spite of these confounding factors there appears to be little dissent from the view that the principal explanation for the observed trends in pharmaceutical innovation lies in the escalating cost of research and development. Of course the nature of pharmaceutical research is such that it is virtually impossible to

Figure 7 *R and D cost per new drug, 1968–70 to 1977–79, £ millions (£s 1980).*



Source Pharmaceutical Sector Working Party, unpublished data.

isolate the costs arising specifically from the development of a particular new drug but available figures make it clear that they have risen substantially above the £2 to £3 million estimated for the first half of the 1960s. In a consultative document published in 1981 the Pharmaceutical Sector Committee (1981) of the Chemicals Economic Development Council reported that the 'cost of developing a successful major drug can now be £50 million or more' (Figure 7). The methodology underpinning this calculation relates a proportion of British companies' research and development expenditure to the number of new drugs launched by these manufacturers over a specified period of time. If the expenditures incurred by the 'failed' research initiatives which unavoidably accompany the evolution of one successful product are also taken into account, this sum may in fact be nearer £90 million (Table 4).

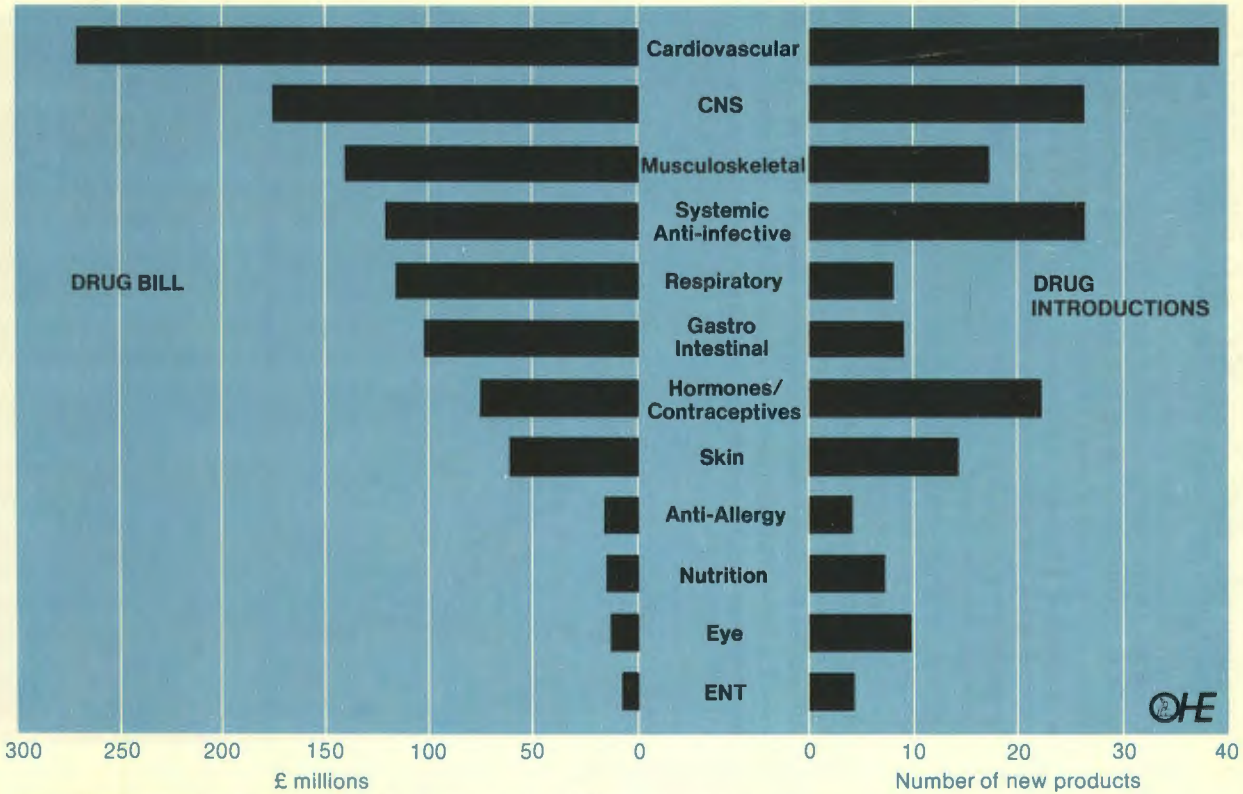
An inevitable consequence of the substantial increase in the cost of pharmaceutical research and development has been a reduction in the number of companies financially capable of participating in the search for novel chemotherapeutic compounds. In addition, even for those manufacturers for whom the latter still represents a feasible strategy, cost escalation has placed a limit on the number of new chemical entities that may be submitted to the development process during any specific period of time. The impact of growing R and D expenditure requirements may also be discerned

Table 4 *Development of a new medical product from discovery to market.*

	Probability of success	*Total cost of successful and unsuccessful R & D*
	%	£m
1. Drug synthesis	—	14
2. Biological screening	0.01	12
3. Initial drug supply	3	0.3
4. Preclinical – first phase	5	24
5. Preclinical – second phase	8	27
6. Initial clinical use	12	0.2
7. Controlled clinical testing	25	5
8. Confirmatory clinical trials	50	4
9. Regulatory affairs	90	2
10. Licensing authority	95	—
11. Prepare for introduction		
12. Introduction		0.4
13. Supervision of product		
14. Product reviews		
		88.9

Source Dench 1981.

Figure 8 *Analysis by therapeutic grouping of the net ingredient cost drug bill in 1982 and new pharmaceutical introductions between 1980 and 1982.*



Note The therapeutic groups shown in the diagram accounted for 95 per cent of the £1,161 million NHS drug bill in 1982 and for 91 per cent of the 194 new products

in the nature of new chemical entities reaching the market. In order to minimise the risks involved in investing vast sums of money in the development of new medicines there has been an understandable tendency on the part of manufacturers to concentrate their efforts on disease/therapy areas where knowledge already exists and market potential is promising. The latter point is broadly illustrated in Figure 8 which shows an analysis by therapeutic grouping of the net ingredient cost drug bill in 1982 and the 204 drugs listed by the Monthly Index of Medical Specialities (MIMS) as having entered the UK pharmaceutical market between January 1980 and December 1982.[1] Partly as a consequence of this degree of clustering in therapeutic areas where medicines are already available – for example, the edition of MIMS for December 1979 included 33 drugs for the treatment of angina and ischaemic heart disease to which a further 11 products were added over the next three years – some commentators have argued that the reduced new drug introduction rate has also been accompanied by a diminution in the innovative novelty of NCEs entering the market today compared with 20 years ago.

Explaining the trends

Whilst there is a broad consensus for the hypothesis that increasing costs constitute the primary explanation for the innovation patterns described above, it is the factors underpinning this cost explosion that have given rise to continuing debate. Of those receiving attention to date, regulatory procedures have perhaps been subject to the most detailed scrutiny. In many economically advanced nations, the genesis of extensive government activity to establish safety standards for new medicines can be traced back to the discovery of the teratogenic effects of thalidomide in the early 1960s. In this country the episode led to the implementation of various voluntary initiatives to oversee the testing of new medicines and their release to the market. In 1968 the latter were codified within the Medicines Act which set up the Committee on Safety of Medicines to function as an advisory body to the Licensing Authority – the agency responsible for granting clinical trial certificates and product licences. Concomitant with the construction and subsequent evolution of this administrative machinery there has been a steady accretion of the

1 Difficulties arising both from the content of these two sets of data and in their interpretation imply that caution is required in their use. For example, the MIMS data are not confined to new chemical entities alone, all new products listed over the three year period are included. Further, some of these products are restricted to use in hospitals yet the drug bill data are only concerned with GP originated pharmaceutical costs. Finally, there are inconsistencies between the therapeutic groupings employed by the two data sources.

testing requirements new medicines have to satisfy before market access is permitted (Figure 9, see centre spread).

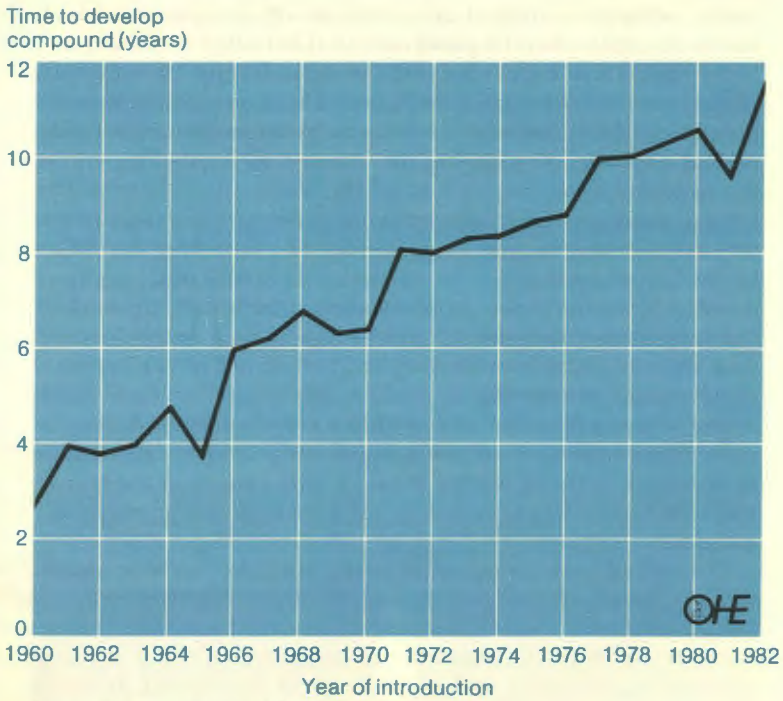
The principal effect of this regulatory proliferation has been to extend the development phase endured by a major new chemical entity in its transition from initial discovery to marketing to a period of ten or more years; in the early 1960s, it was not unusual for a similar project to be completed within a period of approximately three years (Figure 10).[2]

It is axiomatic that additional and more prolonged testing must directly raise development expenditures because of commensurately greater manpower and material requirements. For example, it has been estimated that between 300 and 500 Kg of the new chemical compound is needed today for pre-clinical testing compared with just 20 to 30 Kg in the early 1970s (Newbould 1981). In addition, the number of animals required for routine toxiological testing procedures is now three times that prevailing in the early 1960s. On this particular aspect Smith (1980a) has reported that not only does the necessary high quality of these animals – which may include dogs and monkeys as well as the more usual rabbits, rats and mice – entail a high level of expense but the experiments in which they are employed generate vast amounts of data to be processed. 'For example, in a single standard two year carcinogenicity study in rodents the number of individual observations, raw data and calculations that require to be recorded . . . has been estimated to exceed half a million'. The sum of these and other requirements underpin the observation of Hartley and Maynard (1982) from their 1980 sample of pharmaceutical companies operating in the British market that the documents submitted to DHSS in application for a clinical trial certificate ran, on average, to 1,600 pages.

The imposition of new regulations has also exerted an adverse impact on investment horizons. The prolongation of a potential new drug's period of development has of course been accompanied by a reduction of equal magnitude in the period of patent coverage remaining after market launch. Innovation has therefore been inhibited not only because it requires pharmaceutical companies to tie up ever increasing sums of money over progressively lengthening periods of time but also by the reduction in the opportunity for securing an appropriate return on these R and D expenditures. The extra degree of risk implied by the latter coupled with

2 The link between regulatory growth and extended development times for new drugs reflects administrative delays in the processing of submissions as well as the additional testing and data processing workload. Focusing on the former, data from ABPI submission surveys reported by Walker (1982) indicate that during the second half of the 1970s the delay on the part of the authorities in processing a clinical trial certificate application averaged around 9 months. For product licence applications during the same period an average of 12 months elapsed between submission and formal decision.

Figure 10 *Increase in development times for NCEs marketed in the United Kingdom 1960–82.*



Source Ravenscroft and Walker 1983.

the uncertainties already inherent in pharmaceutical innovation – notably the fact that even the one compound in 10,000 that successfully undergoes screening and development to become a prescribable medicine may rapidly succumb to technological obsolescence – has served to undermine investment confidence.[3]

Yet from a different perspective it has been argued that the deleterious consequences for pharmaceutical innovation inherent in the growth of regulatory requirements should be viewed as the price that has had to be paid to ensure a greater degree of safety for contemporary medicines. Assertions such as these are difficult to evaluate because safety does not in a general sense lend itself to straightforward quantitative assessment. Further, it is a dynamic concept which varies in its meaning and significance under differ-

3 It has also been argued that the extension of development times has had the effect of reorienting R and D budgets towards this sphere of activity at the expense of basic research – Dayan (1981) has estimated that preclinical toxicity testing alone now absorbs between 14 and 16 per cent of R and D spending compared with 8 to 10 per cent a few years earlier – and that this has contributed to the apparent decline in 'major' innovation rates.

ent circumstances. The implied assumption of the regulatory protagonists that intervention via statutory measures is necessary to ensure adequate testing of new medicines is also questionable. It fails to recognise that the pharmaceutical industry's credibility and hence livelihood is founded on the manufacture of only safe, efficacious and high quality medicines. These considerations aside greater emphasis ought perhaps to be given to the more fundamental criticisms surrounding the increase in regulations during the 1960s and 1970s.

First, there has been widespread concern at the extent of the preclinical testing in animals demanded of a new drug candidate. In the 1970s, applications for clinical trial certificates comprised detailed protocols of the proposed clinical trials and copies of all the supporting experimental and biological data. In conjunction with the bureaucratic processing delays referred to earlier, these requirements meant that a considerable period of time might elapse before a potential new medicine commenced evaluation in man. There was therefore the possibility that a significant volume of resources might be wasted should it only emerge at the human stage that there was no point in any further development of the substance.

The risk of such an outcome stems from the fact that animal models are not infrequently a poor means of predicting efficacy and provide only limited information about safety. False predictions may occur for a number of reasons including rapid excretion in animals, differences in their pathways of metabolism, receptor sensitivity and physiology and as a result of the lack of appropriate pathology (George 1980). The syndrome of eye and skin lesions found with regular ingestion of practolol is an example of toxicity not seen in animals. From the opposite perspective animal models may identify problems which do not actually translate to man. Perhaps the best known example in this context is the finding that penicillin is lethal for guinea pigs at low doses. Along similar lines Cromie (1981) has stated that 'current regulatory requirements . . . would have prevented the introduction of aspirin, imipramine, chloroquine, paracetamol and many other standard medicines'.

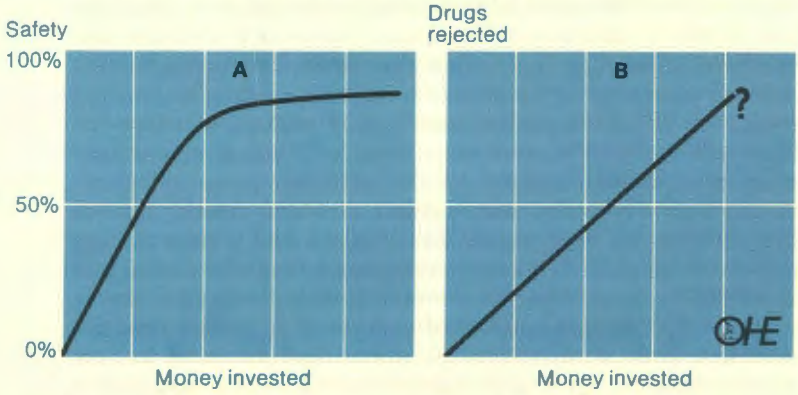
The second major criticism concerns the logic that has underpinned the steady growth of regulatory intervention. Since the thalidomide tragedy the mirage of a perfectly safe drug has dominated public expectations and in response successive governments have nurtured an environment in which regulation has become a self-perpetuating process. Yet new requirements have been implemented (in the absence of any compensatory discarding of superseded procedures) with less regard to their strict scientific relevance than to the belief that safety, or perhaps more accurately risk reduction, enjoys a continuous positive relationship with the quantity of testing that is undertaken.[4]

Erroneous though the latter philosophy may be, it is nevertheless understandable given the desire on the part of the regulatory authorities to play safe in striving to protect the public (*Nature* 1980). In the words of the late Sir Derrick Dunlop (1980): 'Officials charged with approving a new drug can make two kinds of mistakes; they can approve a new drug which turns out to be unexpectedly toxic or refuse one that could have been life saving with few adverse effects. If they make the first mistake their folly will be emblazoned in the public media and disgrace will follow: if the second, few will know of it, and those whose lives might have been saved, will not be there to protest'.

Redressing the regulatory balance

Towards the end of the 1970s there was increasing awareness that the inexorable growth in regulatory requirements coupled with the data processing delays to which this development had inevitably given rise, was having a deleterious impact on pharmaceutical innovation.[5] Reductions in the number and to some extent innova-

Figure 11 *Hypothetical relationships between resources invested in safety testing and (a) resultant 'safety output' and (b) risk of drug rejection.*



Source Walker 1982.

4 It is probable that the law of diminishing returns operates in this context as elsewhere. Thus Walker (1982) has argued that beyond a certain point further toxicity investigations add substantially to the costs of innovation but yield little if any extra knowledge about the safety of a given drug in man. This relationship is illustrated in Figure 11 which also portrays another hazard – namely, that as more tests are carried out the risk of inappropriately rejecting a potentially valuable new medicine increases. Simon (1980) has claimed that it is probable that no drug could be commercialised if all the known tests in all fields were undertaken.

5 This change of opinion was not confined to Britain. In the United States, for example, there was a growing realisation – underpinned by Wardell's (1978) finding that France, Britain and Germany were on average introducing almost three times as many new drugs each year as the United States – that the regulatory system which had 'protected' the country from thalidomide and practolol may at the same time have significantly delayed the availability of effective, life saving medicines.

tive novelty of new chemical entities coming onto the market reflected sustained upward pressure on research and development costs to levels at which only established therapeutic areas with market potential remained viable investment propositions for manufacturers. Thus in 1979 Dunlop wrote that 'inadequate regulation of drugs, which we certainly had before the thalidomide disaster, can prejudice public health, but excessive regulation which we now have can be equally prejudicial . . . .' (See Binns 1981). The following year a leading article in the *British Medical Journal* (1980) warned that 'if present trends continue the pharmaceutical industry, which depends chiefly on research for its prosperity seems certain to run down in the coming decade, with serious direct and indirect consequences. Increasing diversification by the big companies already shows their lack of confidence in the future . . . a growing body of informed opinion holds that the pendulum has swung too far and that the problem must be tackled whatever the difficulties.'

In response to this general disquiet as well as pressure from interested groups the Department of Health has introduced a number of amendments which should expedite the drug development process. The essential feature of these changes is that they link preclinical data requirements on a compound to the amount of clinical testing that is proposed. Combined with further modifications concerning the number of species required for testing and the extent of carcinogenicity and fertility evaluation before the commencement of clinical trials these new requirements take more account than hitherto of the particular drug and target disease that are under investigation and thus herald a more flexible approach to regulation (*Lancet* 1981a). This revised strategy is also complemented by a new exemption scheme for clinical trial approval. The latter supersedes routine formal certification and by virtue of the reduced amount of paperwork it involves and the strict time limits it imposes on the authorities responsible for considering manufacturers' applications should lead to a reduction in drug develoment times. In addition to the beneficial effects these changes will confer upon pharmaceutical investment horizons advantages should also accrue in terms of more efficient research and development expenditure with fewer resources being wasted on projects which have to be abandoned in the human phase but only after extensive pre-clinical investigation.

Other determinants of innovative performance

The modifications to drug testing procedures in the UK and related initiatives currently under consideration in the United States (Hayes 1983) imply official acquiescence with the widely documented view that stringent regulation has been a major disincentive to innovation in recent times. Yet other frequently interlinked

factors have also contributed to the relatively low number of new medicines becoming available each year. The evolution of progressively more sophisticated research techniques, for example, has been one of these factors via a steady upward pressure on the cost of innovation.

Today's new medicines generally originate from a variety of highly scientific processes.[6] One approach involves subjecting chemical entities that have already been synthesised to a battery of tests designed to detect different types of biological activity. An alternative method entails the synthesis and testing of chemical analogues of existing medicines for biological activity. This approach has occasionally been disparagingly dubbed 'molecular manipulation' yet it has produced medicines with novel therapeutic properties (the thiazide diuretics and oral hypoglycaemic agents, for example, stemmed from minor modifications to the early antimicrobial sulphanilamide) and improved modes of actions, including enhanced selectivity and absorption.

A third approach involves the design of substances to fulfil particular biological roles. In one respect this may entail the synthesis of a naturally occurring substance – the dopamine precursor levodopa for Parkinson's disease exemplifies this strategy. Alternatively, the objective may be to develop a chemical analogue of a naturally occurring product in order to modify the effects of endogenous substances. Drugs of this type include the beta-adrenoceptor antagonists employed in angina to inhibit the effects of circulating catecholamines, thereby reducing myocardial oxygen consumption. More recent examples include cimetidine and ranitidine to block the action of histamine on the H_2 receptors and thus, via a diminution of acid output from the stomach, promote the healing of peptic ulcers. Advances of this nature have clearly necessitated the allocation of substantial resources to research aimed at improved understanding of disease processes as well as sustained high levels of investment in the increasingly sophisticated and correspondingly expensive scientific instruments, measuring systems and computers which have made such progress in knowledge possible.

Other explanations for the reduced number of new chemical entities reaching the market each year during the 1970s switch the emphasis away from strictly economic considerations. There has, for example, been speculation that the trend represents a relative

6 Serendipitous discovery and straightforward screening of soil samples for potentially valuable micro organisms have long since been surpassed as major sources of chemotherapeutic advance. Nevertheless the possibility that future contributions might stem from the former, which yielded *inter alia* antidepressant drugs from those initially employed to treat tuberculosis and more recently the tetracyclic antidepressant mianserin from a research programme which had originally set out to investigate the compound's potential as a prophylactic treatment for migraine and hay fever, should not be discounted altogether.

deceleration that had inevitably to follow the unprecedented levels of innovative activity of the 1950s and early 1960s. Whilst there is undoubtedly some validity in the contention that the opportunities for discovering new anti-infectives by screening micro-organisms in the soil were diminishing, new fields of potential advance were opening up.[7] Consequently, any decline in innovation should, at worst, have manifested as a temporary interruption preceding the resumption of a high level of annual NCE introductions. As the data depicted in Figures 4 and 5 indicate this did not occur.

Another hypothesis is that the thalidomide tragedy acted as a catalyst in tempering medical and popular regard for the 'wonder' drugs which in the 1950s appeared to offer the promise of cures for all human ailments. The episode dramatised the potential hazards and uncertainty accompanying new medicines and counselled caution in their use. The outcome was a generally more cautious approach to chemotherapeutic innovation. This stimulated pharmaceutical companies to develop better information regarding safety and efficacy but necessarily prolonged development times and hence reduced drug introduction rates. Thus it can be argued that enhanced 'self-regulation' by the industry led to an 'acceptable' decline in new drug introduction rates but that the latter were subsequently driven to yet lower levels by the imposition of additional and sometimes irrelevant testing requirements and by the bureacratic delays which resulted from the extended involvement of external regulatory agencies in the innovative process.

Some diminution in the number of new drugs reaching the market each year was also implicit in the 'therapeutic transition' that was taking place during the 1960s. Throughout the preceding phase of pharmacological advance anti-infective medicines had, in numerical terms at least, predominated.Their employment usually involves the administration of a short course of treatment which has as its target the removal of specific disease organisms from the body and thus the restoration of health. As a consequence, drug testing was correspondingly straightforward. Since the mid-1960s, however, pharmacological intervention has been increasingly directed at diseases where the goal of therapy, in the present state of knowledge, is the long term prevention or control of symptoms:

7 From an examination of disaggregated innovation trends in the United States, Wiggins (1982) has argued that the overall drop in NCE introductions reflects a specific reduction in preparations acting on the central nervous system as well as fewer anti-infective medicines. Whilst the explanation for the latter trend is based upon technological considerations, Wiggins contends that the former – only 10 new major and minor tranquillisers were introduced between 1962 and 1969 compared with 28 over the period 1954 and 1961 – was the product of several factors including the rapidly established therapeutic pre-eminence of diazepam and chlordiazepoxide which, supported by strong patent protection, 'pre-empted the potential for further improvement in the area'.

'cures' are not yet available. Inevitably, the shift towards treatments requiring prolonged drug administration, as is the case, for example, in the management of hypertension, has been accompanied by a commensurate extension of drug testing horizons.

The foregoing suggests that no one cause in isolation can account for the consistently lowered rate of NCE introduction since the first half of the 1960s. Instead the trend is attributable to a combination of factors, the relative significance of each of which is, and seems likely to remain, a source of contention. One potential explanation for the innovative performance of recent times can, however, be firmly discounted: as the following section will show the possibilites for therapeutic progress still abound even if, given resource constraints, they can no longer realistically be seen as unbounded.

Therapeutic targets for the future

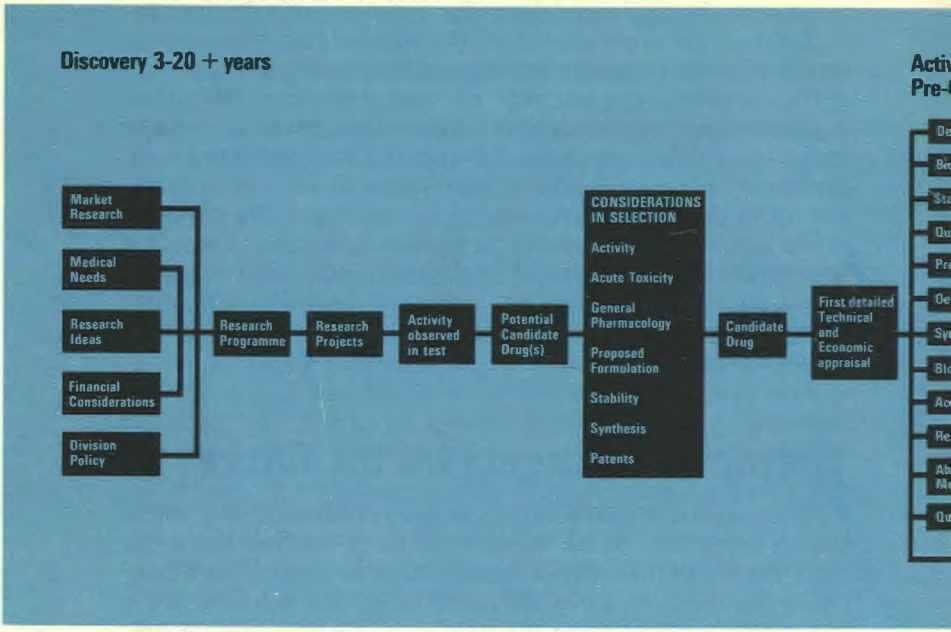
If it is assumed that man possesses an innate biological clock which sets an upper limit to the duration of life of between 80 and 90 years (Fries 1980) then in broad terms it may be argued that society is now confronted by a two-fold health target. The first objective is to expedite a reduction in the number of persons who die prematurely. The second is to minimise the morbidity and disablement experienced by individuals, especially during the latter part of their lifetime. These goals are neatly encapsulated in Doll's (1983) expressed desire to 'die young as late as possible'.

Returning to the first of these aims, the evolving shape of the survival curve shown in Figure 12 indicates that marked improvements have been achieved in life expectancies during the present century. Average expectation of life is however still some way short of the 'optimum' defined above, and further progress is clearly dependent upon a significant reduction in the current volume of premature mortality. Data for England and Wales reveal that there were 578,171 deaths in 1981 and that more than 130,000 of these (that is 26 per cent) involved persons who had yet to celebrate their 65th birthday – a milestone still 5 and 11 years below contemporary average life expectancies for males and females respectively.

More detailed analysis of these data indicates that a significant proportion of premature mortality can be attributed to just a limited number of causes. Thus in 1981, coronary heart disease, malignant neoplasms[8] and injuries and poisonings accounted for

8 More specifically, cancers of the lung and digestive system accounted for 67 per cent of male fatalities under 65 years from malignant neoplasms in 1981. These two sites were less significant for females, being responsible for 34 per cent of premature cancer deaths; the major single contributor was breast cancer (28 per cent).

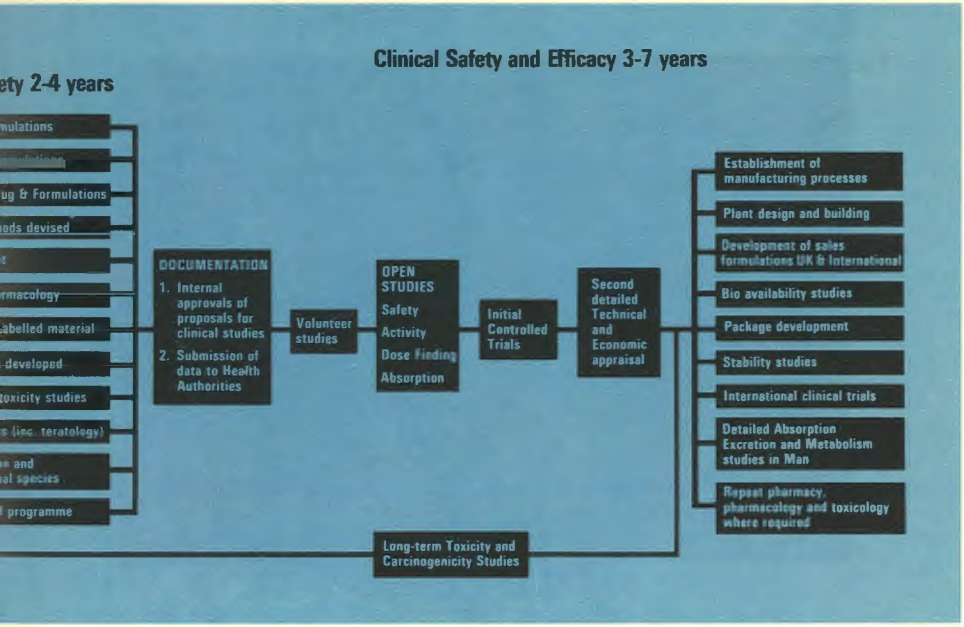
Figure 9 *Stages in the discovery and development of a typical drug. (See page 18).*



Source ICI Pharmaceuticals Division 1980.

70 per cent of male and 63 per cent of female deaths below the age of 65 years. In each of these instances epidemiological investigation has yielded persuasive evidence that 'environmental' factors underlie causation: Figure 13 illustrates, for example, the putative prominence of tobacco and inappropriate diet in the multifactorial aetiology of cancer. These two factors, in conjunction with raised blood pressure and a group of apparently more 'secondary' influences including inadequate physical exercise and stressful lifestyle, are also implicated in the genesis and subsequent evolution of the arterial lesions found in coronary heart disease. Observations of this nature have fostered the now widely held belief that premature mortality is to a large extent avoidable and that progress towards this goal requires appropriate behavioural modification and more effective preventive medicine.

Yet the latter is difficult to achieve. Scepticism about the value of a given preventive measure might persist because of the difficulties of objectively proving its efficacy. Acceptability of any proposed strategy is also a function of the social sequelae, financial issues and opportunity costs perceived to accompany its application (Doll 1983). The net effect of these and other factors may be perpetually to delay the implementation of action and to encourage only an incomplete response to prevention initiatives on the

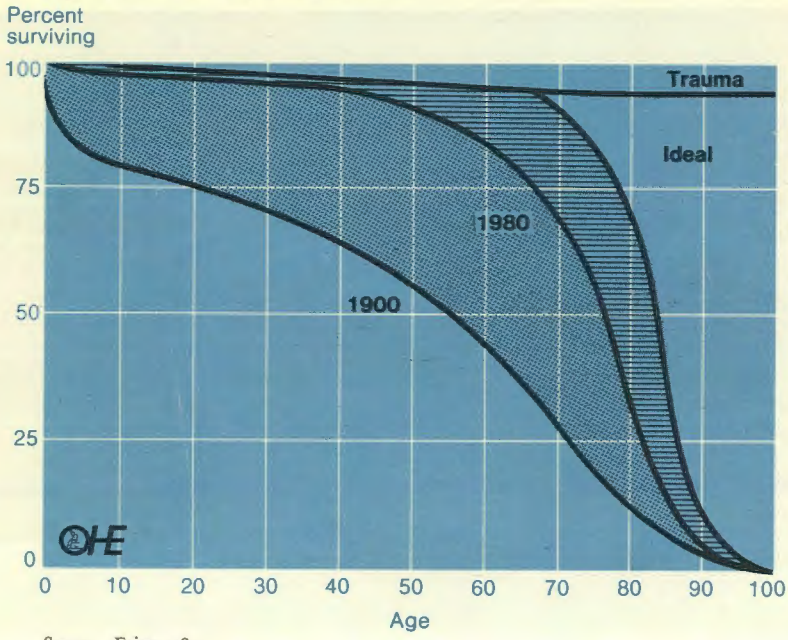


part of the public. Consequently, whilst prevention undoubtedly constitutes the desirable solution to much premature mortality, shortfalls in effectiveness coupled with uncertainty regarding the significance of the approach for other causes of untimely death imply a pressing need for continuing chemotherapeutic innovation.

In the latter respect Doll (1983) has argued that whilst it is inconceivable that a single vaccine could prevent all types of cancer (which resulted in 41,405 deaths under 65 years in 1981) viruses do appear to contribute to the aetiology of some specific tumour types and these may become preventable by immunisation. Examples of the latter might include several cancers that depend on infection with the Epstein Barr virus and cancer of the cervix which appears to be venereal in origin although the identity of the infective agent is still uncertain. Opportunities might also lie in the development and use of special vaccines against, for example, influenza and pneumonia (the specified cause of death of more than 3,600 individuals under 65 in 1981) as well as viral and parasitic diseases. Active immunisation against hepatitis B virus is currently used for high risk subjects and may soon become more widely available.

There is also optimism in the specific context of cancer that

Figure 12 *The Evolving Survival Curve.*

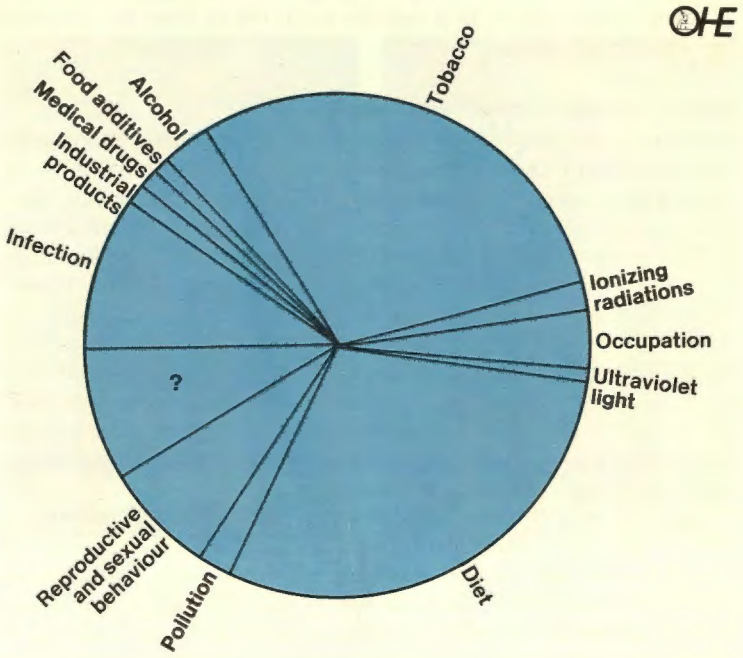


Source Fries 1980.

potential developments in the vaccine field will be complemented by improved means of chemotherapeutic intervention. Progress is expected to stem, for example, from further elucidation of the strategies adopted by cancer cells to promote their own survival (Myers 1983). And new combinations of the 30 or so anticancer drugs available at the present time and other experimental substances should facilitate enhanced control over the dissemination of secondary tumours (Hellman 1983). Finally, the recent discovery of oncogenes represents a major advance in understanding of the molecular basis of malignancy and offers good prospects for the future development of new approaches to anti-cancer therapy (Krontiris 1983).

The prospect that the burden of premature death from coronary heart disease might yield, in part at least, to pharmacological approaches has also been raised by recent research advances. The discovery that the balance between free and restricted blood flow is determined by a complex relationship between thromboxane in blood platelets and prostacyclin contained in the vessel walls generates a number of possibilities for the development of antithrombotic therapy. These include the use of selective thromboxane synthetase inhibitors, the stimulation of endogenous prostacyclin production and the pharmacological reinforcement of

Figure 13 *Cancer mortality: best estimates of the volume attributable to different causes.*



Source Imperial Cancer Research Fund.

endogenous prostacyclin mechanisms by synthetic prostacyclin or a chemical analogue. As far as direct substitution of endogenous prostacyclin is concerned, considerable efforts are now being made to obtain a stable compound which is easier to use and with fewer side effects than prostacyclin itself. 'If this is achieved we can look forward to the availability of potent, orally active compounds for testing as prophylactics or treatments in many types of cardiovascular disease' (Vane 1982).

Potential advances of the type outlined above provide powerful incentives to continued research into what might be designated the technological means of preventing death before the biblically allotted span of three score years and ten. Yet, in the current state of knowledge, it may be optimistic to suppose that future developments in chemotherapy could have an effect on premature mortality that will stand comparison with the impact of anti-infective medication during the 'first pharmacological revolution'. Significant success in this area would appear instead to depend upon the effective implementation of mass health promotion/ disease prevention programmes. However, premature mortality represents only one aspect of the health target identified above; of equal con-

cern are the high levels of morbidity and disablement which persist in the community among all age groups. It is in this area that pharmaceutical innovation may be expected to have its principal impact.

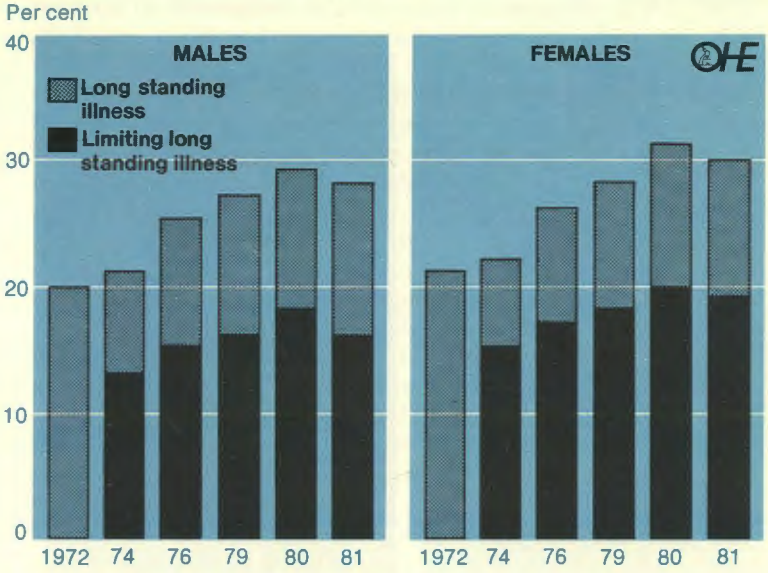
Morbidity: the unresolved problems

Accurate quantification of the potential for reducing the overall burden of acute and chronic illness via therapeutic progress is to a large extent impracticable because of the dearth of appropriate information on occurrence and the limitations of traditional measures of morbidity which are often employed as substitutes. Hospital data, for example, are frequently indicative of disease prevalence only above certain thresholds of severity. Statistics of sickness absence from work have similarly limited value because of their irrelevance for large sections of the population; even among those of working age they disregard individuals whose impairments either prohibit their participation in the workforce or do not affect capacity for work but are nevertheless disabling in other contexts. Data from general practice might be expected to reflect more accurately the level of ill health in the community but this is not necessarily a valid assumption because service demand is a function *inter alia* of the feasibility of therapeutic intervention. Finally the General Household Survey furnishes up-to-date information about the broad occurrence of acute and long standing ill health (Figures 14 and 15) but fails to elicit details of the underlying causes of this self-reported morbidity.

In spite of these imperfections in the available data it is clear that there are many diseases for which therapies are either inadequate at the present or simply non-existent. Within the mental diseases a prominent illustration of the latter instance is provided by senile dementia. This disorder involves irreversible and usually progressive destruction of the brain in old age and is characterised by failing memory, intellectual deterioration and behavioural disturbance. Ten per cent of the population aged 65 years and over (more than 700,000 people) are affected and a revision of previous estimates of the costs of care (OHE 1979) suggests that dementia currently gives rise to an annual level of expenditure exceeding £600 million. Furthermore, demographic forecasts combined with age specific prevalence rates indicate that the burden of care the disorder already imposes on health and social service supports as well as relatives will become more severe over the remaining years of the century.

In the same broad disease grouping potential continues to exist for therapeutic advance in schizophrenia. More people of working age who are in hospital or disabled in the community suffer from schizophrenic illness than any other potentially handicapping condition. In the UK approaching 150,000 persons are affected at any

Figure 14 *Chronic illness: proportion of the population reporting long standing illness and limiting long standing illness, Great Britain, 1972–80.*



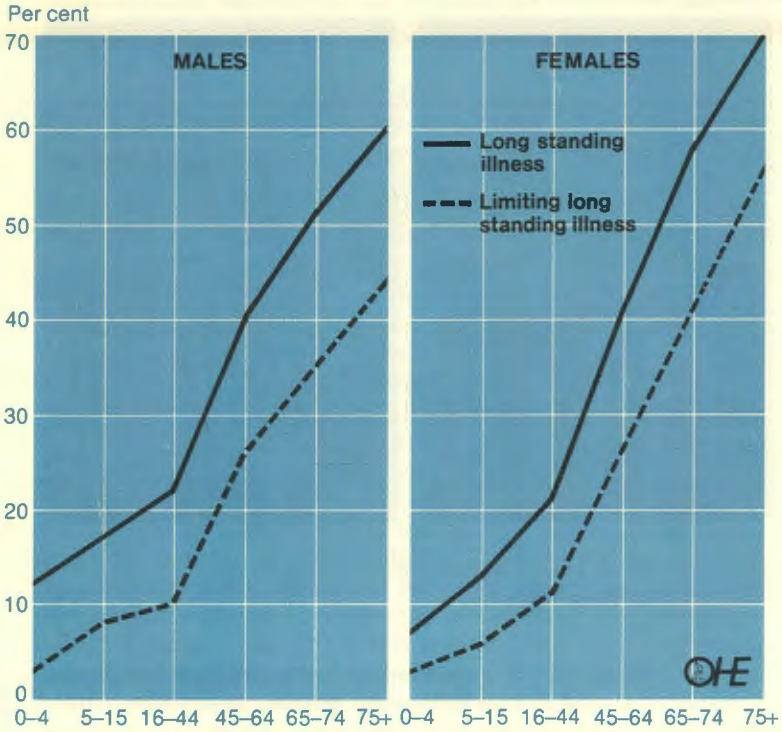
Note Data on limiting long standing illness not available for 1972.
Source General Household Survey.

one time, giving rise to expenditures on health and social care currently estimated at £300 million per annum. Depression, which will be responsible for the hospitalisation in Britain of between a million and a million and a half people in the present population at some stage during their lifetime, is another important target for therapeutic research.

Many neurological illnesses similarly await the advent of improved means of therapeutic intervention. For example, although 85 per cent of patients with Parkinson's disease (which afflicts between 60 and 80 thousand elderly people in the UK) initially respond well to treatment with levodopa, the latter is accompanied by a high incidence of unpleasant side effects and at 5 years only one third of patients are found to be significantly better than before the commencement of therapy (Lawry 1983). This observation clearly highlights the need for continued therapeutic progress; but the case is perhaps even more persuasively advanced in the context of multiple sclerosis.

This disorder inflicts varying degrees of disablement on some 50,000 individuals in Britain and with onset generally occurring in early and mid-adulthood it strikes at a time when family and other commitments are at a peak. Yet in spite of substantial growth in the volume of research endeavours directed at multiple sclerosis –

Figure 15 *Chronic illness: proportion of population in selected age groups reporting long standing illness (——) and limiting long standing illness (– – – –) in Britain in 1981.*



Source General Household Survey.

Current Contents, for example, now lists an average of seven references to the disease every week – the cause of the disorder has yet to be determined, diagnostic methods are controversial, no curative treatment has been found and even palliation is problematical (Matthews 1983). A recent leading article in the *Lancet* (1983) thus summarised the history of treatment in multiple sclerosis as 'one of recurrent claims for success, each enjoying a brief period of enthusiasm but bringing eventual disappointment to sufferers from the disease'.

Focusing on diseases of the musculoskeletal system and connective tissue – which are the cause of physical impairment for approximately 1.2 million adults living in the community – there is no doubt that non-steroidal anti-inflammatory medicines have made a major contribution in the provision of effective symptomatic relief especially in osteoarthritis. Of potentially greater impact would be an extension of therapeutic intervention to those stages in the aetiological chain which precede symptomatic expres-

sion – to prevent or retard the degenerative processes underlying the disease. Equally, there is considerable scope for therapeutic progress in rheumatoid arthritis which accounts for 14 per cent of the severe handicaps experienced by adults of working age. Most of the 500,000 people who suffer the crippling effects of rheumatoid arthritis are however in their sixties or older. Consequently, this disease in many respects exemplifies the type of target that is increasingly shifting towards the centre of attention in medical research: in other words, disorders which are relatively insignificant as causes of mortality or economic burden (measured, for example, in terms of sickness absence from work and hospital costs) but which, given present therapeutic deficiencies, are responsible for considerable personal suffering and social cost.

In broad terms, it is predicted that pharmaceutical research too will become increasingly concerned with resolving the chronic disabling conditions which exert a powerful negative impact on the quality of life not only for affected individuals but also for the relatives and friends involved in their care. The solutions to emerge will extend from 'cures' to new means of intervening to retard disease processes supplemented by more effective methods of suppressing the symptomatic manifestation of disease. The overall effect will be 'to add life to years rather than years to life' and may be illustrated diagrammatically in a manner analagous to that employed for mortality in Figure 12: substituting morbidity for mortality the objective is once again the 'rectangularisation' of the curve so that significant morbidity is delayed in onset until an advanced stage in life and thus compressed in duration. At the same time it is clear that implicit in this target is the further requirement that the impact of pharmaceutical innovation should not be confined to the alleviation of chronic disease alone: progress needs to be achieved in the treatment of episodes of acute sickness stemming *inter alia* from viral infections and in the control currently possible over the sequelae of those diseases which are theoretically preventable but nevertheless remain a prominent feature of contemporary morbidity and mortality profiles.

Ways forward in therapy

Improved control of disease will be dependent in large measure upon the evolution of novel chemotherapies. Yet progress can also be expected to stem from the further development of currently available treatments. Continued experimentation might, for example, reveal previously unsuspected uses for an established drug. In this context a classic example is provided by the beta blockers (Turner 1983). Originally developed to treat angina, these drugs have subsequently achieved 'first line' status in the manage-

ment of essential hypertension. Beta blockade has also been shown to facilitate control of cardiac arrhythmias and to be of symptomatic value in hyperthyroidism.

In addition, these drugs can markedly reduce the tremor associated with anxiety and those which do not possess partial agonist activity are effective in the prophylaxis of migraine in about 50 to 60 per cent of patients. Beta blockers as eye drops reduce intraocular pressure by decreasing the secretion of aqueous humour and in this context timolol has recently been shown to provide effective treatment for chronic simple glaucoma in 70 per cent of cases. Finally, the cumulative evidence from 11 clinical trials involving more than 13,000 patients suggests that moderately prolonged beta blockade following myocardial infarction may reduce subsequent mortality by about 25 per cent (*Lancet* 1982).

Recent initiatives have also demonstrated that modifications to a drug's mode of delivery can generate significant therapeutic advantages. Thus asthma sufferers who have experienced difficulties in using the prophylactic drug sodium cromoglycate in the form of an inhaled powder have benefited as a result of the introduction of a metered dose aerosol presentation. Many medicines can now be administered as a slow release tablet which not only diminishes the gastro-intestinal and CNS side effects associated with conventional delivery but may also aid patient compliance because it permits dosage on a once daily basis. As a final example, the development of a transdermal delivery system for glyceryl trinitrate could prove a valuable innovation for angina sufferers. The new presentation mode enables this highly effective drug to be employed on a prophylactic basis which hitherto had not been practicable because of the unpleasant side effects accompanying prolonged oral administration.

Specific product developments such as these may in fact be seen as part of a broader trend towards a more efficient employment of medicines. Ideally, chemotherapy seeks to deliver a constant drug concentration which represents the optimal compromise between beneficial and adverse effects. This goal is frequently unobtainable, however, because traditional presentation modes give rise to serum drug concentrations which fluctuate significantly between administrations. Sustained release formulations go some way to resolving this problem but attention is increasingly being given to pumps and reservoirs which are sufficiently compact to be worn externally or to be implanted under the skin as a means of providing rate-controlled drug delivery for ambulatory patients. These innovations are generally at an experimental stage but observations to date suggest that the administration of several familiar drugs by sustained infusion may increase their therapeutic efficacy. The programmed infusion of insulin, for example, may offer a more reliable means of correcting the metabolic abnormalities of

diabetes mellitus. Heparin may also be more effective in preventing thrombosis when administered in this manner.

In addition to raising the efficacy of a given drug and reducing its attendant side effects because of the lower concentrations that are possible, some of these sustained release systems also offer scope for greater precision in drug delivery. Thus the use of pumps to perfuse selected sites such as the liver or the central nervous system with anti-cancer agents is currently under investigation.

Obstacles in the form of molecules, cells, membranes and organs which confront a drug on its passage from the site of administration to the target can be an important limiting factor on the potential efficacy of chemotherapy. There is furthermore the hazard that the latter may deleteriously affect the surrounding environment during the course of this journey. Nevertheless, there is increasing optimism that a solution to the problem of accurate and intact drug delivery could be found in the development not only of locally implantable mechanical devices but also of a variety of transporting vehicles. In respect of the latter, a recent review by Gregoriadis (1981) listed more than 30 drug carriers of potential use in medicine. Interest has focused especially on liposomes[9] and more recently monoclonal antibodies (*Lancet* 1981) and Gregoriadis has expressed the view that sustained co-ordinated research programmes should yield new carrier systems which 'will prove useful and, in some cases, perhaps revolutionise therapy'.

Novel routes to therapeutic advance

Over the past few years, international meetings have been concerned with the identification of those areas in which therapeutic advance is most likely to be achieved. Discussions have been wide ranging but there would perhaps be a consensus that one of the most exciting prospects is offered by the deepening understanding of DNA – the genetic substance of all living cells. Although it was initially discovered by the German biochemist Miescher in 1869 it was not until 1953 that Watson and Crick determined its structure to be composed of two chains of nucleotides, intertwined to form a

9 Liposomes are small globules of fatty acids and phosphorous in which drugs can be entrapped (McKenzie and Yanchinski 1983). They can be formed by evaporating a solution of phospholipid in chloroform followed by resuspension with agitation in an aqueous phase. If the latter contains a drug in solution, a portion of this will be trapped within the liposome (Summers 1983). By varying lipid composition and size an almost infinite number of liposome versions can be produced to meet specific goals. For example, high density lipoproteins in the blood remove phospholipid molecules from liposomes to render them 'leaky' to entrapped drugs. Consequently by adjusting the cholesterol content of the bilayers, lipoprotein action can effectively be controlled to achieve either optimum rates of drug leakage from circulating liposomes or intact delivery to a specific target. In general, evidence of the clinical efficacy of liposomes is still awaited although De Silva and his colleagues (1979) have reported that liposomal steroid can produce improvement in synovitis in rheumatoid arthritis employing only one twenty-fifth of the conventional therapeutic dose.

double helix. Subsequent research has provided scientists with a technique – known as recombinant DNA technology[10] – which permits mass production of genetic material.

The potential benefits of this development are legion. The availability of large quantities of a single gene in pure form will facilitate study of the chemical structure and function of normal and mutated genes. This in turn should lead to a better understanding of how defects in these genes can modify their functions and armed with this knowledge it may then become possible to correct inherited disorders. The incidence of the latter is difficult to determine accurately – occurrence fluctuates markedly between communities and there is considerable uncertainty regarding the relative importance of genetic and acquired factors in the aetiology of common diseases such as schizophrenia, manic depressive psychosis, epilepsy, diabetes mellitus and cancer – but Weatherall (1983) has estimated that the figure lies between 2 and 5 per cent of all live births (Table 5). Furthermore these disorders are responsible for a significant volume of morbidity and mortality: they account for about one third of paediatric admissions to hospital, cause 40 to 50 per cent of deaths in childhood and chronic diseases with an appreciable genetic component affect about 10 per cent of the adult population.

These orders of magnitude highlight the potential gains from advances leading to effective preventive or therapeutic approaches to genetic disease. It is therefore encouraging to note that the list of disorders in which the defective gene product is known has risen from 15 in 1960 to over 1,000 in 1980 and that it is currently possible to identify the chromosomal location of more than 35 such mutant human genes (Fredrickson 1981). Disorders originating from a single gene defect are however rare whereas those with a more substantial incidence are probably the result of multiple genetic aberration and will be commensurately more difficult to surmount.

Gene splicing also offers new ways of manufacturing drugs. Human insulin produced by this technique has recently become available furnishing an alternative to the porcine and bovine insulins which have formed the mainstay of therapy since 1922. The

10 Recombinant DNA (rDNA) is a technique by which segments of DNA from different organisms can be broken up and rejoined to form a new hybrid molecule. One method of achieving this involves the use of circular pieces of DNA known as plasmids which are found within some bacteria. Initially, the plasmid is removed from the bacteria and treated with special enzymes, called 'restriction endonucleases' to cause it to split apart. These enzymes are then also used to isolate a piece of DNA containing a specific gene or genes from another organism's DNA. Next, this second piece of DNA is inserted into the plasmid's DNA, after which the recombined molecule is fused enzymatically and returned to a bacterial host. Bacteria that act in this way as hosts to hybrid plasmids then effectively become microscopic factories turning out copies of the recombined plasmids as the bacteria themselves grow and multiply (Hecht 1981).

Table 5 *Approximate load of genetic disease in Northern Europe.*

Type of genetic disease	*Frequency/1000 population*
Single gene:	
Dominant	1.8–9.5
Recessive	2.2–2.5
X-linked	0.5–2.0
Chromosome abnormalities	6.8
Common disorders with a significant genetic component.[1]	(7–10)
Congenital malformations.[2]	(19–22)
Total (approximate)	(37.3–52.8)

1. Genetic contribution: say, one third of such disorders as schizophrenia, diabetes mellitus, cyclothymia and epilepsy.
2. Genetic contribution: say, half of malformations like spina bifida, congenital heart disease, talipes equinovarus, cleft lip with or without cleft palate, etc.

Note The figures in parenthesis indicate that they are, at best, gross approximations.

Source Weatherall 1983.

future prospects are good for other products including endorphins, 'blood products' such as urokinase, serum albumin and clotting factors as well as thymosin and other peptide hormones (Hecht 1981) – indeed the US Office of Technology Assessment reports that there are 38 human hormones that could be produced by genetic engineering (Kreitzman 1983). The latter also yields opportunities for the development of new vaccines against, for example, hepatitis, influenza and polio.[11] But at the present time interferon is probably the best known product of rDNA technology.

Interferons were discovered in 1957 by Issacs and Lindenmann and appeared to be ideal antiviral agents. They are glycoproteins liberated by human cells during virus infection which limit the spread of disease by rendering other unaffected cells resistant to the invading agent.[12]

Discovery of the activity of interferons initially generated the belief that with large scale manufacture these proteins could become the penicillins of virus infections. It is only recently, however, with the advent of rDNA technology and other processes that the production of acceptably pure material in adequate quantities has become possible. Consequently, experimentation has been delayed and with few exceptions the results of clinical assessment

11 In theory genetic engineering should lead to safer vaccines by using microbes to grow just the surface antigen of a virus rather than the complete infective organism.

12 This protection is brought about in a number of ways including the triggering of enzyme reactions in a cell which prevent the virus from using the cell's protein synthesis machinery for its own reproduction.

are still awaited. Nevertheless, the employment of interferons has given encouraging results in a number of virus infections: varicella – zoster (shingles), herpes keratitis, juvenile laryngeal papilloma, chronic active hepatitis and warts. It has also proved successful in prophylactic use against experimental rhinovirus infection (the common cold).[13]

Prospects for the development of effective antiviral chemotherapy – which has proved considerably more problematic than was the case with the antibiotics and other agents for bacterial infection because viruses are active *within* cells so that interventions risk exerting a toxic impact on the host as well as the virus – are no longer founded exclusively on the interferons. Acyclovir, for example, is a recently introduced drug which acts selectively on herpes simplex virus (HSV) infected cells. Although it has no direct antiherpetic activity, it is converted in the cell to an analogue of deoxyguanosine which specifically inhibits the synthesis of HSV DNA. The enzyme responsible for this conversion is coded for by the virus genome and so is only present in infected cells. To date topical acyclovir has proved effective in herpes simplex corneal ulcers whilst systemic administration has achieved good results in the treatment of mucocutaneous herpes simplex infections in the immunocompromised and zoster in normal patients (*BMJ* 1982).

Acyclovir represents a valuable new approach in antiviral chemotherapy and other chemicals that act in a similar way are under investigation. As an alternative to attacking enzymes[14] that catalyse important steps in the viral life-cycle, research efforts are also being directed at finding ways of interfering with the viral genetic material directly (Scott 1983). Yet further endeavours seek to intervene at an earlier stage in the process of infection than the above two strategies – that is, before the virus actually enters the cell. In this context investigations are underway of the feasibility of competitively blocking the receptor molecules in cell membranes with which virus proteins bind to initiate infection. In sum these and other potential approaches underpin hopes of extending the meagre list of currently available antiviral chemotherapies (only three anti-viral drugs appeared in the August 1983 UK Monthly Index of Medical Specialities) in the not too distant future.

13 Interferon is also being evaluated as a treatment for multiple sclerosis. Its experimental use in this disease stems from interferon's role in viral infection and reports of deficient interferon production and natural killer cell activity in peripheral blood and cerebrospinal fluid from patients with multiple sclerosis (*Lancet* 1983). Findings to date have indicated some degree of success in reducing relapse rates but the validity of these observations has been questioned and the results of further clinical trials are awaited to provide clarification.

14 Viruses can contain from one to over 200 genes, many coding for enzymes which perform highly specialised tasks in the viral life cycle.

Interferons in cancer

Early laboratory studies showed that in addition to their antiviral activity interferons could reduce or prevent the development of tumours in mice and other animals infected with cancer viruses. It was later found that treatment with interferon could also protect animals against a variety of transplantable tumours, carcinogen-induced tumours and those arising spontaneously. The optimism generated by these observations appeared subsequently to be justified by the results of clinical application: early preparations of relatively impure interferon were shown to have some effect in causing objective regression of certain tumours. Unfortunately, it soon became apparent that the initial responses tended to be both partial and transient and that increased doses could not resolve the problem because of the serious side effects attendant to the therapy. There was also uncertainty about the role of the contaminants present in these early impure preparations (*BMJ* 1983).

The development of recombinant interferon has circumvented the latter source of confusion by making available very pure material. Many trials are now in progress but findings to date have not been very encouraging; consistent regression of tumours has been observed only in patients with myeloma, non-Hodgkins lymphoma and breast cancer (*BMJ* 1983). (The latter is, however, an important cause of morbidity and mortality: provisional estimates indicate that there were almost 21,700 newly diagnosed cases of breast cancer in 1980 in England and Wales; the same cause was responsible for 12,513 female deaths in 1981, 45 per cent occurring before 65 years of age.) Further, responses generally continue to be incomplete – generating reductions in tumour size rather than total disappearance. In spite of these disappointments the potential of interferon merits further detailed investigation. The latter might especially focus on the potential benefits of its employment at an earlier stage in the disease process or in combination with other drugs. But perhaps the key to unlocking future advance lies in a more precise understanding of the functions of each of the three families of interferon and their numerous subspecies.

Chemical messengers and new therapies

During the last two decades or so there has been unprecedented progress in understanding how the transmission of chemical substances between cells facilitates the functioning of bodily systems and on the basis of this knowledge valuable new therapies have been constructed. For example, elucidation of the stimulatory effects of noradrenaline and adrenaline in the heart led to the development of the beta blockers. A more recent research advance in this field has yielded an inhibitor of angiotensin converting enzyme which offers a new approach to hypertension and a range of other therapeutic applications now recognised to be

more extensive than was initially supposed (Hodsman and Robertson 1983).

Chemical transmitter manipulation has also been successfully employed as a means of therapeutic intervention in Parkinson's disease in which the characteristic rigidity and tremor originate from a deficiency of the neurotransmitter dopamine. The development of replacement therapy for this disorder (involving the administration of levodopa, the precursor of dopamine) has raised hopes that intervention following similar principles may yield benefits in other central nervous system and mental diseases where defects in the neurotransmitter system are of key significance.

The latter may be the case in senile dementia. The precise causes of this disease have yet to be identified but the observation in the mid-1970s of lower activity of the enzyme choline acetyltransferase in post mortem cerebral cortex from patients compared with controls suggested the possibility of a neurotransmitter-specific aetiology. In theory there are two broad approaches to raising acetylcholine levels. One might involve the direct administration to affected individuals of the substance itself, the enzyme involved in its production or one of its precursors. Alternatively, the acetylcholine that is present might be made more effective either by reducing its enzymatic degradation by cholinesterases or by inhibiting those systems which oppose the cholinergic system. Clinical trials based on the former strategy have, to date, achieved limited success. In spite of this disappointment it would seem reasonable to expect that further understanding of the physiology of the cholinergic and other systems in the human brain will make possible a clearer identification of neurotransmitter and receptor abnormalities and thus pave the way for therapeutic intervention.

Schizophrenia is another disease which might also yield to this type of approach. Research suggests that excess levels of the neurotransmitter dopamine in the brain may play an aetiological role in schizophrenia. However, this probably represents an inappropriately simplistic view of the aetiology: dopamine may have a variety of facilitating and inhibitory functions and its effect may differ in relation to the status of the dopamine receptors. Furthermore, there is evidence that other chemical transmitters such as gamma amino butyric acid and abnormalities in noradrenaline metabolism are also of significance. Nevertheless, observations such as these suggest that in the future it might be possible to diminish the mental disabilities and social handicaps suffered by schizophrenics by correcting the biochemical impairments underlying their disease.

Sustained research efforts in the field of neurotransmitters, their precursors and their sites/modes of action can therefore be expected to yield novel therapeutic strategies for central nervous

system and other diseases in the future. In addition new information on brain chemistry might disclose the mechanisms whereby existing drugs exert their effects and thus serve as another input to potential pharmacological advance. At the same time progress seems likely to stem from a better understanding of another broad group of chemical messengers: the regulatory peptides. The latter can be produced and released by both endocrine and neural tissues and may act as circulating hormones, local regulators, neurotransmitters or all of these with a diversity of functions (Polak and Bloom 1983).

Some of the regulatory peptides have a relatively long history: secretin, for example, was identified in 1902 and gastrin in 1905. The majority, however, have emerged during the last two decades and the research leading to these discoveries has also made clear that individual peptides are widely distributed throughout the body's tissues and not confined to specific organ systems. Somatostatin, for example, inhibits the release of growth hormone and has also been found in large concentrations in the gastrointestinal tract and pancreas as well as in the thyroid and other peripheral organs. But perhaps one of the most exciting of recent developments has been the isolation of brain peptides with opiate-like analgesic actions – the enkephalins and the endorphins (Hughes *et al* 1975). This discovery raises the possibility of designing drugs that offer more effective and safer pain control than is currently possible. Potential advances such as these imply that the regulatory peptide system may become a major route of therapeutic intervention in the future (Polak and Bloom 1983).

Progress in immunology

One final area in which important new knowledge has been gained over the past two decades concerns the mechanisms underpinning immune response. The foundations of immunology were laid by the work of Pasteur, Koch, Ehrlich and others around the turn of the nineteenth century but modern concepts date from as recently as the 1960s with the discovery of the general structure of antibodies and the recognition of the role of lymphocytes in their production (Humphrey 1982). It is now known that lymphocytes fall into two broad categories, T – and B – cells. The former predominate and have a variety of functions, notably inducing B – cells possessing receptors for other parts of the same antigen to which the T – cell initially responded to secrete antibody. From this stage 'scavenger' and other cells become involved in a process leading eventually to the destruction of the invading organism. T – lymphocytes also have a suppressor function, impeding or preventing the work of the B – group. Each of the two main lymphocyte groups can be divided into sub-populations with differing structures and functions and these are linked in a complex series of

interactions which are currently only partially understood. Yet further research should clarify these networks and the control mechanisms ensuring integrated operation of the immune system's components, thereby enhancing the potential for effective therapeutic intervention.

Progress might for example be expected in treating certain proliferative disorders of the lymphoid system in which normal cellular development ceases and lymphocytes undergo malignant transformation. Increasing understanding of what controls normal differentiation may eventually produce means of bypassing the maturation arrest or of devising chemotherapy specific to the arrested stage (Humphrey 1982). New approaches to cancer might stem from determining the causes of the impoverished antibody response which fails to prevent tumour growth. It has been postulated that this may be because tumour cell products actually inhibit cellular immune mechanisms or perhaps because they fail to evoke them. Sustained immunological investigation would also appear to be essential to resolving the many different neurological and psychiatric syndromes which follow viral infections. The latter form a heterogeneous group and include acute disseminated encephalomyelitis – the most common demyelinating disease in the world because of the frequency with which it follows measles and other viral infections – and the Guillain-Barré syndrome (Behan 1983). Viral infections appear to induce syndromes such as these via alteration in the regulation of the immune system involving, perhaps, immunosuppression. The latter may result from various processes including, for example, the activation of suppressor lymphocytes and may eventually yield to corrective therapy.

Aberations within the immune system are also responsible for a considerable volume of contemporary morbidity through a number of diseases demonstrated or believed to involve autoimmune mechanisms, such as rheumatoid arthritis. These diseases are usually defined as states in which there is circulating antibody, not against a foreign antigen (for example, a virus) but against some normal component such as part of the surface of a particular cell type (*Lancet* 1983a). Research efforts aimed at a better understanding of the genesis of autoimmune disease are currently following two principal directions. In the first instance investigations are being undertaken of the association between exposure to an infective agent and the subsequent onset of autoimmunity. A link of this nature was first demonstrated for type 1 (insulin dependent) diabetes and is now widely considered to provide the aetiological explanation for multiple sclerosis. The implication of this putative sequence of events is that such diseases may become susceptible to preventive measures.

Apart, however, from pinpointing the initiating agents involved, this approach would also necessitate the identification of indivi-

duals at risk of developing a specific disease and it is in this respect that successful outcomes to the second major line of research would be especially valuable. These investigations seek to elucidate the genetic basis of vulnerability to autoimmune disease and have to date proved particularly fruitful in insulin dependent diabetes. Further research in the directions noted above coupled with continuing experimentation to devise more effective means of modulating immune responses (for example, immunosuppression) without disturbing other systems of the body should therefore provide the basis from which future reductions in autoimmune-associated disability may be achieved.[15]

Discussion

Inevitably, the foregoing review has outlined only a few of the areas where the continued pursuit of research initiatives offers the prospect of valuable therapeutic advance. It is nevertheless clear that the foundations are now being established from which therapeutic intervention might effectively be extended to many of the contemporary sources of morbidity and disablement.

But whether the promises of today's research endeavours will become available as tomorrow's new treatments is more equivocal. Recent trends in pharmaceutical innovation generate some degree of concern. The last decade or so has seen a relative stagnation in the number of new chemical entities introduced onto the market each year. It has, in addition, been argued that the innovative content of these new products, betokened by degree of novelty and enhanced therapeutic potential, has equally changed little over time. Contentions of this nature should be treated with caution: it is axiomatic that the reference points upon which qualitative judgements of progress are founded are ever-changing and thus demand successively more substantial advances if each new development is to match the innovative status of the initial breakthrough. Furthermore, seemingly minor innovative advances, which frequently yield disproportionately significant benefits for specific patient groups, sum over time to more substantial leaps in progress and help to maintain continuity in the

15 Further understanding of the mechanisms of the immune system also seems likely to stem from research into the prostaglandins. The latter have a clearly demonstrable role in mediating inflammatory reactions but there is also evidence that they can have a profound influence on immunological events. The general view is that prostaglandins inhibit T – and possibly B – lymphocyte function (*Lancet* 1981b). And in Hodgkin's disease excessive prostaglandin synthesis appears to be responsible for the observed impairment of immunological responses.

flow of new knowledge.[16] Available data do nevertheless provide some support for the basic criticism, indicating that new chemical entities introduced to the pharmaceutical market in recent times have clustered around three therapeutic areas: non-steroidal anti-inflammatories, medicines for angina and hypertension and chemotherapies for psychiatric illness.

The explanation for these trends is relatively straightforward. Pharmaceutical companies now have to spend between £50 million and £100 million over a period of 10 or more years to bring a major new chemical entity from its discovery in the laboratory to the prescription medicine market. Potential new products can of course fail at any point in the development process and should this occur at a relatively advanced stage, investments running into millions of pounds can be lost. The risks inherent in innovation are compounded by the fact that even after market launch commercial success cannot be guaranteed: the competitive nature of the pharmaceutical market is such that new products may rapidly succumb to technological obsolescence. In addition, diminishing effective patent terms raise the possibility that new medicines may not achieve the sales revenues necessary to recoup research and development expenditures before cheap generic substitution commences. Against this background pharmaceutical companies retaining the capacity to undertake major research initiatives have sought to minimise risk by focusing on areas where there is a well established knowledge base and a market of sufficient size to offer the prospect of a reasonable return on investment. Thus 'the tendency has been to try and improve on what is already available because there is no compensation for firms that go bankrupt in attempting to provide socially desirable, but uneconomic products' (Binns 1981).

Research programmes adhering to this philosophy are clearly unsuited to fuelling the take-off and subsequent evolution of a potential new era of therapeutic progress. Central to the fruition of the latter is, therefore, the creation of an environment which is propitious to truly innovative endeavour. In part this will require a commitment on the part of central government to adequate and sustained funding of basic and applied medical research undertaken in academia. It will also necessitate a continued fostering of the relationships between scientists working in these settings and their industry based counterparts. The major prerequisite is to ensure that the regulatory, economic and social circumstances within which the pharmaceutical industry operates as the essential

16 It should also be emphasised that despite the general trends described in this paper a number of major innovations have emerged in recent years including, for example, calcium arnagonists, cyclosporin, angiotensin converting enzyme inhibitors, new generation cephalosporins, histamine H_2 receptor antagonists, the imidazole group of antifungals and the retinoids.

vehicle of new drug development are compatible with the notion of innovation as a viable commercial objective.

Focusing on regulatory procedures, attention has been drawn in this paper to recent initiatives designed to infuse greater efficiency and relevance into the testing and approval process. Future requirements are, however, difficult to predict. Novel chemical substances and therapeutic approaches to disease might be expected to give rise to more onerous testing needs, especially if the former entail prolonged patient exposure. A compensating trend might, however, result from developments in drug delivery technology. Thus the employment of rate-controlled methods of administration might promote a higher survival rate for potential new medicines undergoing evaluation, especially perhaps among those possessing greater potency and lower therapeutic ratios. In spite of this uncertainty, it may be postulated that the more flexible approach to regulatory requirements implied by the outcome of official re-assessment in this area over the past few years should remove at least some of the disincentive to innovative activity which prevailed throughout the 1970s.

Enhanced rationality in this respect is unlikely, however, to lead to overall reductions in the cost of bringing new chemical entities to the market in the future: savings that do result will probably be counterbalanced by the increased expenditures necessary to explore new therapeutic terrain. Consequently the commercial acceptability of major research and development programmes will be determined by the perceived scope for recouping investment outlays. In practical terms this means that future progress in chemotherapy is intimately linked to appropriate price levels for pharmaceuticals, unimpeded market access, freedom to disseminate product information and adequate patent coverage. It is therefore important in view of the long lag times inherent in drug development, that government should make explicit an underlying philosophical commitment to pharmaceutical innovation and eschew superficially attractive short term expedients designed to constrain public expenditure which in reality generate only questionable economic benefits and, more seriously, undermine investment confidence.

In order to attract the long term economic support necessary for drug innovation from the public sector – the ultimate purchaser in the monopsonistic market for medicines – it will of course be necessary to demonstrate that investment in pharmaceuticals represents a cost effective method of deploying highly constrained public monies. Yet from a methodological point of view this has become an increasingly difficult task. Previously, quantification of the economic benefits generated by the use of medicines was relatively straightforward: the resultant reductions in mortality, hospital admissions and sickness absence from work were readily con-

verted to financial expression, revealing substantial savings over the costs of the required chemotherapy. The thesis of this paper is, however, that pharmacological progress will manifest as a consolidation of recent trends and increasingly give rise to new medicines whose essential bearing is on the quality of life. Thus the benefits of chemotherapeutic advance will take the form of social or psychological gain leading to more normal functioning whilst advantages of a purely financial nature will become markedly less conspicuous.

The transition to the predicted new era of therapeutics is therefore going to generate a concomitant need for more appropriate methods of representing the benefits of medicines. These new measures can then be employed in justifying the economic imperatives of pharmaceutical innovation which imply the possibility that the proportion of total NHS resources absorbed by the drug bill will in the future exceed the hitherto consistently maintained level of approximately ten per cent. At the same time, more relevant means of portraying the 'social' gains of chemotherapy have an equally valuable role to play in placing the disbenefits which occasionally accompany medicine consumption into an appropriate perspective. To date, the difficulties of quantifying these advantages and their inherently un-newsworthy nature in contrast to the in-depth media investigations usually forthcoming in the event of, say, the discovery of an unsuspected adverse drug reaction, have tended to cloud understanding of the special issues surrounding the use of medicines and diminished public perception of the need for sustained drug innovation. Unless these distortions are redressed there is a danger that they will deleteriously feed back to the regulatory and economic prerequisites for innovation noted above, with the result that the bright prospects for future therapeutic advance will fail to come to fruition.

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