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ASSESSING THE EMPIRICAL EVIDENCE ON THE COSTS AND BENEFITS OF DEVELOPING NEW DRUGS - A GLOBAL PERSPECTIVE

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Innovation: yesterday, today and tomorrow

It is, I believe, very appropriate that when we set out to consider the role of health technology in the world, as we are doing today, we begin by taking a hard look at the entire process of drug development. A great many of the advances in health during the twentieth century involved the introduction of new medicines, and those medicines continue to occupy a major place in medical practice. It is also a fact that most of these new medicines have been introduced under the auspices of the pharmaceutical industry – an immensely powerful and research-based industry that during the last few decades has become increasingly consolidated into a relatively small number of massive and influential organizations of global significance. It would therefore seem logical to begin thus morning by examining the postulate that this process, and the structure which underlies it, has been both medically and economically successful and that it will continue to be successful and significant in the future, no matter what other types of medical innovation may emerge as this new century progresses. We need to look at the costs that this innovation involves and the benefits that it confers on society, and for both purposes we have to devote some attention to the mechanics of the entire process. This latter point is important; there are some significant differences between the way in which industrial drug research was conducted in 1950 and, the way in which it is carried out at the present day, and it seems very clear that the process of innovation will continue to change as we move further ahead. If we do not take account of this ongoing process of change, we run the risk of drawing conclusions and making predictions based on a situation that no longer exists.

One more general point: on all the matters that we need to discuss here there is controversy and there are contradictions regarding both facts and figures. Too

many people have a vested interest in these things for it to be otherwise.

The costs of research and development

Let me then plunge into the problems at the deep end and try to answer the question: what does it cost to develop a new drug? In principle it should indeed be possible to calculate, for any newly introduced medicine, the costs that have been incurred in its creation and evolution; the development process is complex but it consists of finite steps that are meticulously recorded in laboratory journals and books of accounts as part of the scientific process. . It is surprising then to find that even within individual companies where one has sought to make this calculation one encounters doubts and frank contradictions on the matter. When I was working on new book on the pharmaceutical industry some two years ago I interviewed a great many people who worked inside the industry – as I once did myself – and who knew it well. The people were in senior positions, the conversations were confidential and on many matters I was given information that is not generally available to the public. Yet none of these people – and I repeat that – *none of them* was able to give me any clear idea as to what it had cost to discover and develop a recent product from their companies. Either the company itself genuinely did not know, or else the calculation had been made and withheld from its own senior staff. The best that they could do was to refer me to some of the general published data on the costs of drug development of which I was already aware, and of which I shall say a little more presently.

So much for a perhaps naive attempt to get concrete and reliable data on individual drugs. If one seeks to adopt a broader approach and calculate the average discovery and development costs of new drugs in industry as a whole, the puzzles become even more convoluted. The source most generally cited on that score is the Center for the Study of Drug Development, located in a building at Tufts University in Boston, Massachusetts. So what do they say?

Well, in November 2001, that Center released a report in which the average costs of research and development for a new medicine were estimated at \$ 802 million (Tufts 2001); it republished the data later on the *Journal of Health Economics* (Tufts 2003). It has been widely quoted and discussed and it led one American author to produce a critical book under the title *The Eight Hundred Million Dollar Pill* (Goozner 2004), while many others have questioned its conclusions. That Tufts report is now six years old and it was naturally not the end of the story. A little later I was reliably informed that a figure of \$1.2 billion was now being quoted at meetings, based apparently on further oral

statements from the staff of the so-called Tufts Center. And only three weeks ago I heard a figure of no less than \$1.8 billion, based apparently on a statement from an industrial consulting firm; the firm does not appear to have collected hard data of its own, basing its conclusions on conversations with company representatives and I suspect in part a further extrapolation from the Tufts figures. Let me however set those apparently second-hand figures aside and return to the 2003 Tufts estimate that it costs \$802 million to discover and develop a new drug. How reliable are those figures?

The Tufts Center, as it is commonly called, was founded by Dr Lou Lasagna at the University of Rochester, NY in the nineteen sixties, moving to Tufts in 1976. From the start the Center was financed primarily or exclusively by the research-based industry and saw it as its mission to undertake policy studies which could support the industry case on various contentious issues. During its early period it produced multiple and influential studies to support the view that the Federal Food and Drug Administration was excessively slow and ponderous in its approval of new drugs. From 1987 onwards In 1991, the Center released various estimates of the costs of research and development in the United States. (DiMasi 1991) As Goozner summarizes the technique that had been employed, citing the original authors:

“In the initial study, released in 1991, they randomly picked ninety-three new chemical entities under development at a dozen big drug companies and asked the firms to report their research-and-development expenditures on each stage of development for each molecule. They then divided the total expenditures by the number of drugs in the group that eventually gained approval from the FDA - thus factoring in the price of failure - to come up with an average cost per new drug. Their first study pegged the total cost per new drug at \$114 million (measured in 1987 dollars). (Goozner 2004 at p 237).

Doubt may be thrown on those starting data, particularly because the estimates provided by the companies were not subjected to rigid control and standardization; The “Tufts” work through appears in fact to have been based on a highly selected sample of costly drugs (Angell 2004, 43-44). What is more, in view of the purpose for which the study was being undertaken, all parties had an interest in producing estimates which were as high as possible. Much more doubt arises with the way in which the data were then interpreted and extrapolated to come to publishable figures, then and later. No-one would criticize adjustment upwards for inflation, or calculations effectively obliging successful drugs to bear the costs of unfruitful projects. However, more dubious techniques were also used, here and elsewhere, in order to flatter the

figures. Some have pointed out that the “Tufts” estimates make no allowance for tax rebates (a valuable by-product of research investment that effectively reduces the burden on the industry very considerably). A rather obscure formula was applied to allow for the increasing complexity of research, especially particularly that associated with the long-term study of drugs for chronic and degenerative diseases. The cost of clinical studies by industry has been estimated generously at \$2500 per patient as contrasted with documented costs of only \$750 per patient in cancer trials sponsored by the National Cancer Institute (GAO 1999). I might also mention the fact that at an early phase, as Goozner points out, the Center adjusted the costs upward so as to calculate the opportunity cost of capital. As you know, this calculation is based on the consideration that the money invested in research and development today, which would not have a payoff for many years down the road, and could during that time could have been spent on other things or turned back to shareholders as additional profit. This is an entirely valid procedure for an organization faced with a decision as to whether it can afford to undertake high-risk research or not, but it is questionable whether it can validly be used in retrospect to decide what research actually has cost, particularly since it virtually doubles the figures. I would not go into such detail for our meeting were it not for the fact that estimates like this – culminating in 2003 at \$820 million per drug, have been so widely quoted and relied on. So have occasional statements emanating from industry in Europe, such as a declaration by a major Swiss firm that the development of a new drug costs a billion francs (Humer 2005).

To be fair, I should add that although critics of industry have come with some much lower estimates of the cost of drug development, these figures too can be very uncertain.. In the United States, the Public Citizen/Congress Watch organization set the average cost per new drug at no more than \$ 71 million (Public Citizen, 2001), an estimate which was in turn firmly rejected by the industry association. Marcia Angel voices a suspicion “...that the real cost per drug is well under \$100 million” (Angell 2004, 46).

Faced with such dramatic divergences in the figures, from \$71 million to \$1.8 billion, I must at the very least conclude at this stage that we do not really know what it costs on average to develop a new drug, and that the real costs for any individual drug, though they could well be calculated, are simply not available to us. We urgently need to correct that situation. Without hard and verifiable data any debate is useless and likely to be misleading.

The current benefits of drug research to society

I will turn back to the research process in a moment, but first let me say something about the *benefits* of new drugs to society. One needs in particular to draw a conclusion as to how well the industry is currently serving the ideal expressed by Harvey Bale of the International Federation of Pharmaceutical Manufacturers' Associations, and I quote him literally, that "The primary societal responsibility of the pharmaceutical industry of the pharmaceutical industry is to discover and develop new drugs and vaccines." (Bale 2005)

In principle, the benefits of a given drug to a given patient can perfectly well be calculated in economic terms; even the quality of life can be expressed in terms of dollars and cents if necessary, though those are not the only things that matter. But even here there is a right and a wrong way of doing things. In one of the first cost/benefit studies that I ever saw, some thirty years ago, an attempt was being made to justify the unusually high price then being charged for the first H₂-blocker, cimetidine, for the treatment of peptic ulcer. Quite correctly, the authors examined the costs of non-drug treatment for the same condition (essentially involving surgery to remove part of the stomach wall); they calculated the costs of the surgery, hospital care, rehabilitation, loss of working time, permanent partial disability and so on. They then compared these expenses with the costs of three months of cimetidine treatment at the proposed price, and concluded that the latter was fully justified. Unfortunately, the British Medical Journal concluded at that same moment in an editorial, that the drug treatment was likely to be required for a great deal more than three months and that the comparison with radical surgery was not a black and white one. This was an example of an unsatisfactory cost/benefit study, but, such studies can be (and sometimes are) done very well, especially where a serious attempt is made to factor in considerations of quality of life; these naturally must include positive elements (such as rehabilitation) as well as negative (drug side effects).

Cost/benefit studies can also be carried out at the societal level – nationally or within a given community or institution. Here as a rule the benefits will be set primarily against the price paid for the drug. Australia, with its Pharmaceutical Benefits Scheme, some years ago developed a sophisticated method for evaluating the societal benefit of a drug in financial terms as a means of assessing applications for the approval of a starting price. A new drug that provides no clear added benefit, as compared with existing drugs, in terms of efficacy or safety will not be allowed a price any higher than the mean for any existing drugs in its class; a drug that really represents a step ahead will be

allowed a premium price – an excellent method of rewarding innovation, though industry has been quick to argue that the assessment inevitably involves a degree of subjectivity, and that the process of incremental improvement is all too easily overlooked.

This sort of work, carried out in various ways and places, soon leads one to the conclusion that in very recent years we have not as a society enjoyed a great deal of much added benefit from the introduction of new drugs, however emphatically their virtues may be proclaimed. To take a common condition such as hypertension: in the course of sixty years we have experienced just three significant advances: the thiazide diuretics around 1955, the beta-blockers around 1965 and enalapril and its congeners around 1975. Each has been followed by the appearance of numerous congeners having no particular virtues but nothing else has happened and there has been no real breakthrough since – merely a flood of variants and fixed combinations that from the medical point of view have really brought us no further. Much the same can be said about drugs for the treatment of rheumatoid arthritis and other inflammatory conditions, in which further advances are badly needed. A lot of physicians and patients still swear by aspirin, that was introduced in 1899. The fifties and sixties brought some useful alternatives, notably ibuprofen, naproxen and indomethacin. Again, the forty years since then have really brought us nothing better; yet in a comparative study of drug markets in the eighties the number of anti-inflammatory drugs permitted on sale in the liberal Italian market was no less than 50. (Dukes and Lunde, 1981) Yes, there have been at least two noisy campaigns to proclaim the introduction of treatments supposed to provide new breakthroughs in this field – namely Lilly's benoxaprofen and Merck's Vioxx^R. The Lilly drug was withdrawn within a year after it had killed two hundred elderly patients by damaging the liver. The Merck drug was around for a decade until it was found that it was inducing heart disorders and evidence was advanced that the company had been concealing the fact for a long time. The result? For treating the inflammatory symptoms of rheumatoid arthritis we are, despite all the effort, essentially still where we were more than a generation ago, though perhaps a little sadder and wiser.

This obviously raises the question whether industry had been sufficiently successful in maintaining the innovative process as a whole. Spokesmen for the science-based pharmaceutical industry argue that it has not only assumed a large part of the task of serious pharmaceutical innovation in the modern world but also carried it out successfully over a long period and given value for money. Critics on the other hand allege that, especially in the recent past, and despite its extensive resources, industry has delivered far too little relevant innovation to justify either its position or its prices. Company management

will obviously be most inclined to approach this question from the point of view of the number of saleable drugs emerging from the research division over a period of time, and especially the number of highly profitable breakthroughs that have been achieved. Industry in its most ebullient mood is capable of coming with extraordinarily generous estimates. Take this current statement by America's Pharmaceutical Industry:

“Since 1990, scientists have discovered and developed over 300 completely new medicines, vaccines and biologics...” (PHRMA, 2007a).

Expert views differ on how many really new or useful items have entered medicine over the last ten or fifteen years, but some people in the know would probable set the real number at between ten and twenty. The figure of 300 items seems to represent no more than the number of separate items approved by the American Food and Drug Administration over that period, most of which are merely new to the administrative system and in no serious medical sense innovative. Marcia Angell has cautiously adopted a combined quantitative/qualitative approach to the introduction of new drugs in the United States during the five years 1998-2002, the most recent period for which exact figures were available, paying especial attention to products which at the time of submission were selected for “priority review” by the Federal Food and Drug Administration because of what was considered at the time (sometimes a little optimistically) to be their potential significance in advancing medicine. To cite her literally:

“Altogether 415 new drugs were approved - an average of 83 per year, Of these 133 (32 percent) were new molecular entities. The others were variations of old drugs. And of those 133, only 58 were priority review drugs. That averages out to no more than 12 innovative drugs per year, or 14 percent of the total. Not only is this yield very low, but over those five years it got worse. In both 2001 and 2002, only 7 innovative drugs (that is, new molecular entities with priority review) were approved each year, as compared with 9 in 2000, 19 in, 1999 and 16 in 1998.” (Angell 2004 at pp 54-55)

One must be cautious about drawing conclusions as to trends over such a short period, but Angell's analysis at least indicates the meagre overall output and the high proportion of new medicines which contributed very little or nothing to therapeutic progress. Even among those accorded regulatory priority, as Dr Angell herself goes on to point out, not all by any means delivered on their early promise; the only real breakthroughs during that period related to a small number of drugs which were generally “last-ditch” treatments of value in a tiny group of patients with rare conditions or in whom other drugs had not proved effective. Such medicines have an extremely limited sale and could not have been the intended output of major research programmes. When indeed one examines their history, insofar as it is known, they prove as a rule to have been by-products of research which had been intended to achieve a much more

ambitious goal but which failed in its original purpose. That is naturally of itself an important finding, reminding one that drug research, however well planned, cannot be rigidly steered in a particular direction; it is however important to determine what the original intention was, and whether that reflected a genuine ethical commitment by the pharmaceutical industry to tackle the real challenges facing medicine.

Britain's Parliament established four years ago requested a Select Committee to examine the extent to which research in this field was proving innovative. It heard a great deal of evidence and clearly attempted to be optimistic but it did not really draw a clear conclusion. It noted for example with some appreciation that in the USA, over the preceding decade, the Federal Food and Drug Administration had classified between 23% and 54% of new drug applications as sufficiently promising to merit a degree of priority in the assessment process, but it was elsewhere forced to note, like Marcia Angell had done, that these figures hardly reflected the real proportion of drugs constituting therapeutic advances. Dr Richard Nicholson suggested to the Committee that under 10% of drugs licensed were truly innovative, while Britain's *Drugs and Therapeutics Bulletin* noted very few genuine innovations for patients and a progressive decline in the true innovation rate. (HOC 2005, para. 118)

An examination of drug withdrawals can also be informative when we set out to measure research achievements, since too many of the new products which pass the regulatory barrier subsequently pursue a brief and disastrous career, sometimes doing more harm than good. As the American Lawyer Dan Sigelman has noted, not one of the 13 new drugs in various fields withdrawn for safety reasons in the USA over a decade left a therapeutic gap; in some cases more than a dozen usable alternatives remained (Sigelman 2002)

Some of the discrepancies that one finds in one statement and another also reflect the selective use of data from various periods, chosen because they suit the writer's case particularly well. That is simple, for not only has the research process changed in character over the years but its achievements have oscillated markedly, as shown in Figure 1.

This diagram, published by Achillades and Antonakis a few years ago, gives an impression of the way in which the rate of pharmaceutical innovation varied during the late twentieth century, with two peaks around 1960 and 1985 and a dramatic fall thereafter. The figures used are not exact and the reasons for these variations do not concern us here, though we may wish to spend a little time discussing them presently; they illustrate well the historical drama and in

particular some of the reasons for concern at the present time.

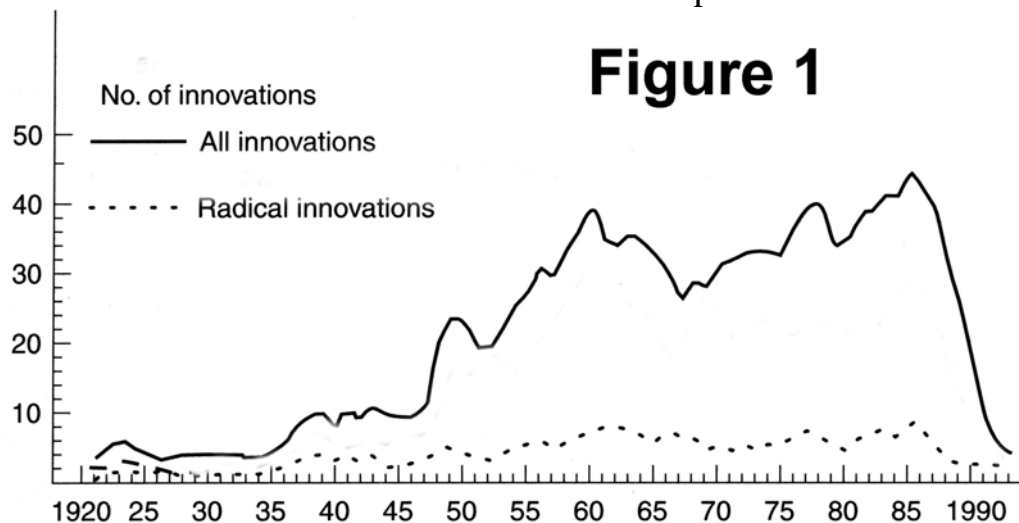


Figure 1: Drug innovation 1920-1990
(Achillades and Antonakis 2001)

Industry has been very prone to blame the introduction of drug regulation for the decline in research, but I have yet to see any evidence that regulation has killed anything more than third-rate drugs, while it has saved many lives. Something like 30% of new drug applications are rejected because they do not meet reasonable standards of quality, safety or efficacy. (Dukes, 1984, 72-5)

Research as a justification for price levels

Turning for a moment to the costs of research as an argument for maintaining the current price level of branded drugs, we can start from the Australian experience to which I already referred, where a technique was introduced to assess the acceptability of prices in terms of social benefit and contrast it with some events in the rest of the world. I was able some time ago to examine the data on three of the products that Australia categorized as non-innovative and thus undeserving of a premium price. In all three cases, these same drugs were being sold at such premium prices in a number of other countries, backed by claims that their creation and development had been so costly. If it is fair to generalize from this very small sample I would suggest that it provides evidence that something is very wrong. A claim that a drug has been so expensive to develop surely needs to be supported by verifiable documentation on the matter. If the claim is not substantiated then it must fail. If it is substantiated, society will have to decide whether it is prepared to support the ongoing research process by paying more for a non-innovative drug than it is really worth in health terms. This is however at present little more than beautiful theory, since pharmaceutical firms simply do not provide the authorities or other with

sufficient evidence to justify the argument that research costs justify high prices. Quite apart from that, one is bound to be skeptical on the matter because there is plenty of reason to believe that high prices reflect entirely different factors. I base that statement on various official documents that give us some insight into how pharmaceutical corporations do spend their money, on matters other than research. The data provided by American companies to the Securities and Exchange Commission are particularly intriguing. As published by the Commission and quoted by WHO and others, the figures for 1999 relating to the ten largest American pharmaceutical corporations are as shown in figure 2:

Figure 2
1999 Pharmaceutical Company Data
for the ten largest U.S. Pharmaceutical Companies

	REVENUE	Cost of Goods	Marketing & Administration	R&D	Profits
	<i>billions</i>	<i>% of revenue</i>	<i>% of revenue</i>	<i>% rev</i>	<i>% rev</i>
Average	\$ 17.557	28	32	13	16
Maximum	\$ 32,714	54	46	20	27
Minimum	\$ 10,003	18	16	6	9

All data from SEC 10K filings and 1999 company annual reports as cited by W.H.O. (Laing 2000)

The percentages speak for themselves. To take only the averages on the first line: these companies were stated to be devoting 13% of their turnover to research, but 32% went to marketing and administration (which naturally includes advertising) and 16% to profit. If one takes these figures at their face value, then one can at once conclude that it is not research that accounts in the first place for the prices of medicines. The sum spent on research is only a third or a quarter of what goes to marketing, administration and profit. But – as in so many other matters - it is not sensible to take even these apparently authoritative figures at their face value. With great respect to the Securities and Exchange Commission, it takes a great deal of such information on trust and is not really capable of verifying it. To take a single example: a company

is very likely to classify as “research” various activities that do not really fall into that creative category. There is for example the so-called “promotional research” that involves supplying practicing physicians with samples of a new drug and requesting them to record their experience with it in their patients; this is not a scientific activity producing useful data, and the intention is primarily to accustom the doctor to using the product, but it is readily classified as “research” in the returns to the Commission. Precisely the same goes for various forms of market research, designed to assess the commercial potential for a product. If one were to exclude such data it is more than very likely that the discrepancy between scientific and commercial activity will be even greater than the figures in the table suggest. What is more, that activity is likely to become ever greater. Research is indeed a relatively risky business, whereas advertising and promotion have time and again been shown to produce profits reliably. Those who have compared the two have repeatedly found that, from the commercial point of view, the rate of return on money spent on advertising medicines is far higher than that on money invested in research. It is hardly surprising then, to find that the amount of money spent annually by a US firm on advertising a drug to the public alone may substantially exceed the sum likely to have been involved in creating it (Mukerjee, 2005).

One more word about the real costs of research – and this may seem a surprising sideline in view of the remainder of my argument. In at least one respect the figures provided by the industry for the costs of research may actually be too low. I am thinking here of the fact – to an important extent – new drugs are now emerging on the basis of discoveries made and initiatives undertaken in an academic environment – in other words outside industry and at the taxpayer’s expense. A firm acquiring such a product will naturally expect to pay certain royalties, but these are the subject of hard negotiation, and in that process the commercial body may well be at an advantage. Only three weeks ago I was listening to an academic speaker whose University had provided the basis research that led to one of the cancer breakthroughs of the eighties. The drug, further developed and sold by a major corporation at an extraordinarily high price, became one of its main sources of profit. I have heard that corporation argue vehemently in court that its pricing and its maintenance of a patent monopoly reflected the need to recuperate the vast expense incurred in its creation. Yet here was the true originator demonstrating to a scientific meeting that his university had earned a mere pittance as a result of the drug’s success, whereas the corporation had benefited to the extent of billions. (Tallahassee, 2005) More importantly, the taxpayers had not been rewarded at all.

The appropriateness of research

Yet another aspect of this complex scene relates to the question as to whether research, as currently undertaken by the pharmaceutical industry, is truly attuned to society's needs. Even within the developed world one can validly put that critical question and demand a truthful answer. A little earlier I contrasted claims that 300 new products had been created over a given period with other estimates that only a handful of these had really benefited society. The others largely represented the ongoing replacement of one drug by another, and then by yet another, in a manner that must at least be characterized as unnecessary or misleading and at worst as wasteful or dangerous. The wasteful development of "me-too" drugs on a massive scale is by no means a new phenomenon: When Silverman and Lee examined the US market in the early seventies they encountered more than 200 sulphonamides, 130 antihistamines and nearly 100 major and minor tranquillizers. Most of the newer members of these fields, as they remarked, offered the physician and his patient no significant clinical advantages. (Silverman 1974) In each of these fields it would be fair to say that at most a dozen products would have met all conceivable needs, and one might wish that the effort devoted to devising the remainder had been directed to true innovation rather than imitation. What is more, the most spectacular commercial successes in the western market during the last decade have relate to drugs that cure no disease at all, but are merely calculated to raise sexual activity and enjoyment; no doubt they have their place but their dominance in the market is both ridiculous and pathetic, and above all a sad reminder that the competitive market does not currently appear to be driving research primarily in the direction of true health benefit.

That message is a hundred times clearer when one turns to consider the case of the developing world. The United Nations Millennium Report on Access to Medicines notes that "between 1.7 and 2 billion people worldwide have inadequate or no access to life-saving essential medicines." (UNMP (2005) at page xi). Part of that problem is naturally due to difficulties with pricing and distribution but the remainder reflects the fact that pharmaceutical innovation during the twentieth century devoted very little attention to the needs of the developing world. Two Swedish workers estimated that between 1975 and 1997 some 1223 new chemical entities were found to have useful pharmacological properties but that of these only 13 – about 1% - were for treating diseases predominantly prevalent in poor countries. (Byström, 2001). One can argue that this is understandable, since the pharmaceutical industry cannot expect to find a profitable market in poor populations, but it is nevertheless a problem that society has to solve. Not all those conditions are in any case localized tropical diseases. The neglected conditions include malaria

and tuberculosis, both of them conditions the primary treatments for which have encountered problems of drug resistance, so that effective drugs of a new type are urgently needed. Tuberculosis in particular represents a global threat, since resistance organisms can rapidly be disseminated worldwide.

To quote that splendid organization, Doctors without Borders:

“...Tuberculosis kills roughly two million people every year..... but at least 4% of all TB patients worldwide are resistant to at least one of the current first-line drugs. Multi-drug resistant TB, defined as resistance to at least rifampicin and isoniazid, the two most powerful TB drugs, might be spreading as fast as by 250,000 – 400,000 new cases each year. Their treatment relies on “second-line” TB drugs that have far lower efficacy and require even longer administration periods (18-24 months) with much higher cost and much higher rates of adverse effects.” (MSF, 2001)

As many of those working in behalf of developing countries have noted, the industry's choice of priority areas for its research amounts in effect to a deliberate decision to emphasise the ills of the affluent, since these are the patients who have the means to purchase new drugs. On occasion, when this is pointed out in debate, the industrial representative points out that all these conditions also exist in the third world, so that the research in question can be said to be tackling global problems. It is of course true that hyperlipidaemia and erectile dysfunction do exist in the developing world as well as in the west, but they pale into insignificance as compared to the problems presented by still incurable tropical disorders or by infections the causal organisms of which have become resistant to existing drugs.

A whole series of international initiatives, including public-private ventures and non-profit research institutes, are now developing to tackle hitherto neglected problems like this, at least on a limited front, and the coming years will determine how successful or otherwise these can hope to be. But the very fact that these new approaches have been needed shows how very imbalanced the situation has been up to the present. Even the most vigorous champion of pharmaceutical innovation cannot claim that it has served the global community well.

The changing face of research

Finally, let me pull together some of the evidence on which I have cited already regarding the fact that the face of pharmaceutical research is changing. As I remarked already, one must beware of examining present and future issues on

the basis of past performance where one is going through a process of structural change. That is very clearly the situation with which we are faced at the present time. When the Tufts Centre was established by industry to undertake work on research and prices it represented an industrial world with a very well defined research pattern. While, as always, some research projects in industry started with theories drawn up by chemists and pharmacologists as to how a particular advance might be achieved there was also a heavy reliance on mass screening. Large numbers of compounds were synthesized rapidly and examined in animal studies for possible activity; others were brought in from the chemical industry where they had been created in programmes concerned with matters ranging from dyes and flavourings to paints and emulsifiers. A large firm might employ a thousand staff on these ventures and breed massive numbers of experimental animals. Some argued that any smaller organization was doomed to failure – at the time I was myself managing an industrial research unit with some 600 staff, and we sometimes viewed ourselves as only minimally adequate. Much of that has changed. Mass screening of random substances has virtually disappeared; far more sophisticated methods are in use to create tailor-made drugs. At the same time, new biotechnological approaches to the creation of new drugs are being exploited, largely by very small companies specialized in this field. To an increasing extent, large pharmaceutical companies are coming to rely on these as a source of innovation, limiting their own activities to developing these substances up to the stage of marketing and then launching them. In addition, some major innovations have been initiated in Government and State laboratories – such as the National Institutes of Health in the United States and various academic laboratories in Europe, and these two have been followed by industrial development up to the marketing stage. These are not marginal developments by any means: public statements on behalf of industry have confirmed that by 2002 the Pfizer company was earning some 30% of its revenues from licensed innovations and Merck as much as 35%. (Naik 2002)

What all this means is that the mechanics of drug innovation are changing quite rapidly and that we simply cannot extrapolate from the past to determine how things are likely to develop during the next two decades or more, either in terms of performance or of expense. And again one sees how misleading information is sometimes given precisely by selection of facts and the use of old data. Here is PHRMA again:

“Only one of every 10,000 potential medicines investigated by America’s research-based pharmaceutical companies makes it through the research and development pipeline and is approved for patient use.” (PHRMA 2007b).

That may be an approximation to the truth in the days of mass screening – though I doubt whether even at the time figures higher than 1 in 3000 were ever documented - but if anything like it were true today it would be a damning indictment of the inefficiency of the research process.

Some of the ongoing changes to which I have pointed are so new that we do not know how significant they will be; there may be plenty of surprises in store as regards the sort of initiatives that will meet the world's needs in this century.

Discussion and conclusion

It must have struck some of the participants in this meeting, as it has struck me, how in recent weeks and months there has been an accumulation of concern regarding the pharmaceutical state of the world, reflected among other things in meetings, publications and new initiatives to bring about reform. Prices, limited access to medicines, so-called disease mongering, other promotional activities, the political pressure exercised by industry and other serious matters are all in discussion, but the structure, state and direction of research is one of the major sources of concern. The overall situation of that research at the present day also raises major ethical and policy issues that need to be examined objectively and without prejudice. An acute controversy has developed, facts have been selected and distorted to support diametrically opposed points of view and as a result it has become unclear to many whether industrial drug research is on the right course for the coming century or not. Even something as basic as industry's defence of strong patents as a means of encouraging and rewarding research is now under attack; you will find serious writers and agencies advancing evidence that (and I quote one of them literally):

“....current patent law discourages drug companies from developing new drugs by allowing them to make excessive profits through minor changes to existing pharmaceuticals” (ACS, 2006).

That is not a red revolutionary speaking; it is America's prestigious General Accounting Office, speaking in 2006.

With contradictions like that on all sides, we are faced with more uncertainty than ever as to what must be done to render research optimal for the community that it is supposed to serve. Some of the effort currently underway to bring about change could result in a renewed wave of innovation, but they could also result in drastic changes in the costs and structures involved.

We must beware of simplifying the issue. Any discussion of the costs of medicinal research is naturally likely to dwell heavily on the expenses involved in attaining dramatic breakthroughs in therapy, but one must not forget that if research is to serve both the community and the industry properly it must achieve other things as well. It is perfectly true that in some areas incremental improvements in efficacy and safety over a period of time may be as desirable as sudden breakthroughs; many cytostatic drugs are for example much too toxic for the patient and if one can progressively develop analogues that are better tolerated much will have been achieved. The commercial rewards of developing slightly improved derivatives of existing drugs are likely to be less than those resulting from breakthroughs, but so as a rule are the risks, and there is always the small hope that even among these unexciting compounds one may find the occasional jewel. The ultimate face of a company's research and development programme is therefore likely to be largely the resultant of an attempt to balance out these three competing approaches; alongside the daring hunt for blockbusters one will need to find capacity to create some less exciting items) and retain sufficient flexibility to profit promptly from incidental, serendipitous brainwaves. Even that is not the entire picture. A research and development division will also be expected to deal with some problems arising with older products which may need to be reformulated or upgraded and to evaluate ongoing projects offered on licence or on collaborative terms by other firms or institutions.

The ultimate question is bound to be whether, in this complex situation, the pharmaceutical industry is capable of changing its structure and behaviour so as to serve society better as regards innovation in its chosen field of activity. My personal belief, after very many discussions with people in and around that industry, is that it can, if it can contrive to enter into an open and honest discourse with the rest of the community. The industry is allergic to outside interference, but when one approaches it the right way it seems increasingly open to dialogue. In talking frankly to its people I have further developed my respect for both those actively engaged in research and for the senior managers engaged in, matters of broad policy. Many of them realize that there is an urgent need for change. I confess that I have much less respect for those individuals who, all too often, are chosen to represent the industry to the outside world and who selectively interpret data to press home traditional points of view that are by now outdated and unhelpful, sometimes with a scant regard for the truth. The time for propaganda is past. Although on many matters we still struggle with an inadequate insight into the real facts, there is a tremendous swell of opinion now to the effect that the time for real reform has come. Society has both the brains and the billions to bring about a true pharmacological revolution in our time; it is a dream that can be brought to fruition if we are all convinced that its

time has come.

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