MEDICAL PRACTICE

The Drug Industry

The goose that lays the golden drugs

TONY SMITH

Those of us born before the second world war have seen the civil aviation industry blossom, bloom, and virtually die. The immediate postwar period saw dozens of independent companies competing to develop new designs in a period of rapid technical innovation as aircraft progressed from piston engines to turbo-props and jets. Airliners grew bigger and better and more expensive, until the time and money required to take a new design from drawing board to commercial use became too much for all but a handful of companies. One by one the former giants went into liquidation; the few remaining survivors rely heavily on government aid and subsidies.

The same insidious process seems now to be affecting the pharmaceutical industry, which is finding that progressive increases in both the time and money required to take a new drug from the laboratory to commercial use are stifling innovation. Like the aircraft industry, the pharmaceutical industry is becoming dominated by fewer, larger companies. Only a handful of countries—the United States, Britain, West Germany, Switzerland, Belgium, France, and Italy—have companies active in innovative research, and their output is declining. Before the year 2000 the flow of new products may virtually have ceased if nothing is done. This is the first of a series of articles taking an independent view of the evidence of that decline in innovation and looking at contributory factors and possible solutions.

Fewer or better drugs?

Compared with the 1960s, when 250 or more new products were put on to the British market each year, the decline has been dramatic: nowadays (1976-80) the number hovers around 100 per year. The same pattern is seen in other major drug-

producing countries. Furthermore, many of the new products are unsurprising additions to therapeutic groupings already well supplied with effective drugs such as beta-blockers and minor tranquillisers. Some commentators have claimed that the decline has mostly been in new formations and drug combinations and that the rate of introduction of new chemical entities has remained constant at around 15-20 a year in the past decade. In a review in *Nature* earlier this year Steward and Wibberley¹ argued that before drug regulatory agencies imposed their controls many new drugs were put on to the market too early in their development. They justified their assertions by a detailed analysis of the fate of new chemical entities introduced in Britain in the period 1960-75 (see fig 1). The proportion of these new products later withdrawn from the market (because of the appearance of unacceptable side effects, lower efficacy than expected, or simply poor market performance) showed a progressive decline from 1964 onwards—in parallel with the controls introduced under the Medicines Act. They claimed, indeed, that tightening up the controls over the introduction of new drugs had had the desired effect: the compounds coming on to the market were those with important clinical indications and clear advantages over existing remedies, and all had had full scale clinical testing.

Doctors working in the drug industry accept that some of the decline in the rate of introduction of new drugs is attributable to better testing, so that fewer withdrawals are necessary. But they are very disturbed at the decline in true innovation. Everyone to whom I talked thought that if current trends continue clinicians will eventually be deprived of the flow of new drugs to which they have become accustomed.

Large markets only

Dr Richard Rondell (director of clinical research (Europe) at Bristol Myers), for example, sees the number of new chemical entities falling because companies are reluctant to make the long-term investments required except for the few drugs with

very large potential markets such as for peptic ulcer, hypertension, and heart failure. "Companies are now reluctant to make the long-term investments necessary. If I look at the marketing activities of many of the major companies the trend is to go for large markets such as the treatment of hypertension and to say that even if we get one or two per cent of that market that is probably the best way to get a return on investment."

FIG 1—Pharmaceutical products introduced into the United Kingdom 1960-79 (reproduced by permission from *Nature*, 1980;284:118-9).

Nor are these opinions confined to the drug industry. Dr J W Dunne, at WHO in Geneva, took an equally gloomy view of the future for drug development. "The costs of developing a new drug, and the risks involved, are now such," he commented, "that the industry will inevitably focus down on drugs that have an obvious market potential right from the outset. The screw is biting harder and harder." One ominous pointer to future trends was that many firms were backing out of the vaccine field—again because the costs and the risks had become such that they outweighed any possible commercial returns. These trends might not yet be fully apparent, he went on: there were still plenty of drugs under development and in the pipeline that were on the drawing board seven or eight years ago. "But the lack of new drugs will become apparent within the next five or six years. Fewer and fewer therapeutic fields will have any appeal to the research-based pharmaceutical industry; more and more drugs will be introduced that are substitutes for those already on the market in order that a patented product should remain available."

The problem is most apparent in the case of drugs for rare diseases, commented Dr Paul Janssen (president, Janssen Pharmaceuticals). "Take a rare condition such as mucocutaneous candidiasis. At the moment we are studying its treatment with ketoconazole and we have treated something like 90 patients in the United States. The total number in the country suffering from this terrible disease is only around 400—so we shall have wiped out the condition before we have accumulated the data required by the regulatory agencies. I could list 50 or more diseases of this kind for which we know the treatment but in which it would be pointless for us to embark on the process of satisfying the legal requirements: it would be easier to give the drug away."

No place for serendipity

Clearly many drugs and most diseases fall between the extremes of mucocutaneous candidiasis and hypertension: but even in this middle range research directors are finding that they are developing fewer new chemical entities. "A lot are withdrawn by the companies at an early stage," said Dr Robert N Smith of Roche Products. "The expense of preclinical testing means that if we are working with five chemical analogues we may decide we can afford only to take one of these to the stage of studies in man." Such a policy goes against all the history of drug development, which was studded with examples of compounds proving to have unexpected, species-specific properties which had turned out to be of great clinical importance.

Nor is there much prospect of new drugs coming from other sources. No useful innovations have come from the Iron Curtain countries. Certainly up to and during the second world war new drugs came into medical use from several sources other than the major drug companies. Between 1935 and 1949 only 52% of new drugs were originated by the pharmaceutical industry; 34% came from universities and academic institutions and the rest from a scattering of other sources. Even in the "golden decade"—1950 to 1962—which saw the introduction of the major antibiotics and so many other drugs, the industry produced 69%, universities 16%, and other sources 15% of new drugs. Industry's share of the much smaller output is now over 80%.

Time lag

Yet at the same time that industry has become almost the monopoly supplier of new drugs its own research groups are losing confidence in its ability to continue successful innovation. At the heart of this loss of faith is the steady lengthening of the time required to get new drugs through the development phase so that they can begin to earn some money. The time lag between the first publication of a paper on a new drug and the first marketing of that drug has increased steadily from a few months in the early 1950s to about five years in the mid 1960s, seven to eight years in the mid 70s, and nine to 10 years now (fig 2).

FIG 2—Time lag between first publication and marketing (adapted from Cromie BW, in *Medicines for the Year 2000*; Office of Health Economics, London 1979).

These delays (and their causes will be analysed in greater detail later) have several effects. Firstly, they make drugs more expensive. As Dr Smith said: "You have to look at costs in two ways: the absolute costs of developing the drug and the period of patent life which gives the company the chance to get a return on its investment. An extension of the development time

from five to seven years not only increases costs at that end but also cuts two years off the effective patent life and so erodes profitability." Little wonder, he went on, that chemical companies were no longer investing or diversifying into pharmaceuticals: in the past few years their financial advisers had seen pharmaceuticals as an area of diminishing returns.

Secondly, the delays have a depressing effect on morale within research departments. Indeed, Dr Janssen thinks that this effect is more important than the increase in costs. "The system makes more and more people believe that nothing is possible any more. They get demotivated because young researchers in the laboratory see themselves as victims of a kind of dictatorial bureaucracy." Young research workers like to be able to see some practical results within—at most—three or four years of the start of a project. The current time scale was such that they might have to wait 10 years—and that seemed a lifetime to a man in his 20s.

Cynics and critics of the drug industry might say yes, fewer drugs are being developed—and fewer companies are in the business of innovative research. Might this not be simply because the drug boom is over? The 20 years after the second world war were enormously fruitful for the pharmaceutical industry, as an apparently endless stream of antibiotics, diuretics, hypotensive agents, corticosteroids, contraceptive steroids, tranquillisers, and anti-inflammatory drugs poured out of research departments. Companies built up whole research departments with skill in one or two of these areas, exploring every possibility of molecular manipulation and almost every ball seemed to hit a coconut. Might not these research departments have had life too easy for too long, grown too large and complex, and simply become fossilised, with no one having the courage to break into new territory?

Certainly, Dr Smith agreed, most companies have skill in a particular area and tend to stay within that narrow confine. "It would be a very brave company indeed which said it had come to the end of the road and would break up, say, its cardiovascular team and go into gastroenterology. It is rather like the car industry. You tool up to get your graduates, your technical staff, and your equipment, you establish your methodology. Once you have an expert team assembled, like all academics they want to push their research further and improve it. They will rarely strike out into entirely new, unfamiliar ground." The trend has been for research organisations to get bigger, more expensive, and perhaps less flexible. This change has been inevitable in the view of many medical scientists as a result of advances in pharmacology and toxicology. "Emphasis is put excessively on the drug regulatory agencies," says Dr J Gelzer, of the international research department of Ciba Geigy in Basle, Switzerland. "The regulations are one restraint, but the whole drug innovation process has become much more sophisticated in the past 20 years. Take, for instance, a class of drugs as familiar as the beta-blockers. No one can come up with a new drug that is less well investigated than those currently available." Dr Rondell echoed this view. "I am not sure," he commented, "how much of the increased time required for clinical research relates primarily to regulatory requirements and how much is due simply to changing views in the medical profession and in industry—on what it is reasonable to do with a drug before you present it to the profession for marketing.

Nevertheless, there was no shortage of new ideas. "If the pharmaceutical industry were free to operate in a less restrictive way and at less cost in the terms of developing new compounds," said Dr Rondell, "it might not be necessary for a company to produce another beta-blocker." There were plenty of new areas awaiting exploitation. Dr Janssen believes, for example, that the drug industry is only beginning to investigate areas such as immunopharmacology—a view echoed by the other research directors to whom I spoke. Better understanding of neuroendocrinology, gastrointestinal functions, and the pathogenesis of many of the chronic diseases would be expected to lead to whole new families of drugs—if the research required

was seen as cost effective by the industry. Dr Gelzer was not as pessimistic as some of his colleagues. "I think innovation will continue in close linkage with progress in basic biology—physiology, pathophysiology, and biochemistry," he suggested. "No matter how difficult or boring it becomes to push a drug through all the regulatory channels, the excitement will remain so long as we see—for example—a chance of tackling allergy in a more rational fashion."

Combination of factors

No one disputes that prescribing doctors are seeing fewer new drugs now than 10 or even five years ago; and no one challenges the assertion by the pharmaceutical industry that the rate of innovation seems likely to decline. What is less certain is the relative importance of at least four causes. Some of the most profitable classes of drugs have now probably come to the end of their major commercial potential—antibiotics and minor tranquillisers, for example; technical advances and consumer pressures have made the process of drug development more elaborate and costly; drug regulatory agencies have added substantially to these costly delays; and governmental control of the prices charged for drugs has reduced profitability. All these factors are now combining to force pharmaceutical companies to look for new products only in therapeutic regions with huge market potential, but the drug regulatory agencies have been singled out by some of the industry as one of the main causes of their difficulties. How far that belief is justified will be discussed next week.

Reference

- 1 Steward F, Wibberley G. Drug innovation—what's slowing it down? *Nature* 1980;284:118-20.

What health hazards, if any, can occur if the family's pet dog swims in the garden bathing pool?

Coliform organisms are to be expected around the animal's anal orifice, and these and other intestinal bacteria might therefore contaminate the water in the pool. There is a remote risk also of contamination, from time to time, with salmonellae and dysenteric organisms. Accidental swallowing of the water containing these organisms could give rise to acute enteritis, salmonellosis, or dysentery. Possibly the dog might contaminate the water with ova of *Toxocara canis* or, very rarely, *Echinococcus granulosus*. Again, accidental swallowing of contaminated water might be expected to be a source of infection with toxocariasis or hydatid disease.

Should a person bitten by a dog be given antitetanus treatment?

Tetanus is known to have occurred after snake bite, and administration of tetanus toxoid is a standard procedure after such bites have been sustained. The mouths of herbivores might, from time to time, be expected to be contaminated with tetanus spores, and, even though records of tetanus after bites of herbivores are difficult to find, it would be prudent to administer tetanus toxoid to those who had been bitten by such animals. Dogs and other carnivores are less likely to have tetanus spores in their mouths, but it must be remembered that any deeply penetrating wound may result in tetanus if tetanic spores had been present on the bitten skin. Such contamination is particularly likely to occur among farm workers but any who have been in contact with soil might, under these circumstances, be predisposed to the infection. On grounds of caution and prudence, therefore, tetanus toxoid is recommended for those who have had any deeply penetrating wound whether caused by an animal bite or other trauma.