

CURRENT SCIENCE

Volume 78 Number 8

25 April 2000

EDITORIAL

Drug research: A growing gap

The costs of developing a new drug keep escalating as the research behind the discovery of every new candidate molecule becomes ever more sophisticated and the regulatory process becomes more stringent and long drawn out. An estimate made some years ago suggested that it costs as much as 500 million dollars (Rs 2000 crores) to develop a single successful product. There are lower estimates, but these would only scale down the cost by a factor of two, at best. The costs, of course, include the expenses of following many false trails. In order to keep ahead of the competition multinational pharmaceutical companies need to make huge investments in research and development; an imperative that has catalyzed many mergers in the drug industry. The marriage of Glaxo Wellcome and Smith Kline Beecham has created a behemoth, with an estimated revenue last year of \$23.6 billion and an annual R&D expenditure of about \$3.7 billion. But, if these figures look large, the Pfizer-Warner Lambert alliance seems to have created a competitor for the position of champion R&D spender; with the research budget of \$4 billion from a total revenue of \$29.1 billion. (To help readers, who like this writer find conversions difficult, 1 billion dollars translates to approximately Rs 4000 crores.) In analysing the spate of mergers a recent article sums up succinctly: 'being the biggest kid on the block has become the hottest game in town' (B. Agnew, *Science*, 2000, **287**, 1952).

But why is research aimed at new drug development becoming so expensive. After all Alexander Fleming discovered the antibacterial properties of mold secretions serendipitously; although it did take a few years and the skills of Ernest Chain and Howard Florey, spurred on by the exigencies of wartime, to produce penicillin in the 1940s. Did not Edward Jenner produce the almost magical smallpox vaccine based solely on his keen observation of the resistance of milkmaids exposed to cowpox? Was not Pasteur's rabies vaccine discovered with little investment? Is it not a fact that aspirin, so widely used today, has had many of its beneficial effects discovered accidentally over the course of a century of use? Unfortunately in modern times the process of drug discovery has become more complex, the criterion that must be met before human use has become extremely

strict and the range of diseases for which therapeutics are sought has widened dramatically. The thalidomide tragedies of the 1960s provided a lesson that will not be forgotten. Today any new and promising molecule must pass through several phases of testing to detect toxic effects before approval for human use. These procedures cost both time and money.

An obvious corollary of the high cost of drug research is that companies will invest only in R&D activities, that ensure the highest returns if a successful product emerges. Research in the areas of diabetes, hypertension and cardiovascular disease, central nervous system disorders and the ailments of old age and cancer among others, may have the highest chances of a pay off, with large, anticipated markets in the developed world. In contrast, many 'Third World diseases' like malaria, filariasis, leishmaniasis ('kala azar') and a host of others may be poor targets for attack. Even if a successful therapeutic is developed, the possibilities of recovering the costs of R&D and turning a tidy profit are poor. Focusing on diseases which afflict a large population steeped in poverty, can hardly be considered as a viable strategy for a pharmaceutical company driven by the imperatives of the market place. The recent resurgence of tuberculosis research in the West may be traced directly to the reemergence of the disease in the developed world, in the wake of immune suppression in AIDS victims. The emergence of drug-resistant strains adds a new dimension of urgency. The fight against the orphan diseases of the Third World has sometimes benefitted from the munificence of rich governments subsidizing the costs of private R&D and from a few acts of philanthropy by large companies; African river blindness and trypanosomiasis ('sleeping sickness') are two examples, where successful therapeutics have emerged from multinational R&D laboratories. But, it is unlikely that future struggles against the diseases specific to the Third World can rely exclusively on well-intentioned charity.

What is the situation in drug research in India? The pharmaceutical industry in this country has grown on two strengths; synthetic chemistry and chemical engineering. Clever process development has permitted the economical production of well-known drugs, under the

umbrella of patent laws which do not allow protection of molecules; the process patent and not the product patent has allowed cheap, legal production of bulk pharmaceuticals. Understandably, multinational companies which invest hundreds of millions of dollars on R&D have always felt cheated; but most often these companies have engineered abnormally high prices in their own native markets, pleading high costs of production. But the rules of the game are set to change soon, as the implementation of the TRIPS agreement will result in the protection of product patents in India. This sceptre has seen Indian pharmaceutical companies enhance their R&D spending; but no single company in India has the financial muscle power to even imagine competing with the multinationals. The pragmatic strategy appears to be the hope that R&D efforts can result in some leads, which can then be licensed to major international companies, which in turn will then underwrite the costs of future development. The Third World's basket of diseases are unlikely to attract much support in this scenario.

As in most other spheres, thus far the Government has been the major supporter of research in the area of drug development. Several national laboratories and academic institutions have ongoing programs in this broad area; the Central Drug Research Institute, Lucknow serving as the flagship of this enterprise. But, as in other areas, the sheer pace of advance in biomedical research has left Indian institutions completely in the lurch. From a field which relied predominantly on chemistry, pharmacology and clinical sciences, contemporary drug research requires major inputs from fast moving fields like genomics, structural, molecular and cellular biology, which constitute the fundamental core of modern biotechnology. The rapidly developing methodologies of combinatorial chemistry and high throughput screening, which are at the heart of the new paradigm of 'irrational drug discovery' are still largely unknown and unpractised in India. The level of technological accomplishment in the laboratories is primitive, handicapped as we are by a lack of resources and more importantly, manpower of the right kind. The cutting edge of drug discovery research is a confluence of several disciplines, which bud off from the major streams of chemistry, bi-

ology, physics and computer science. This interdisciplinarity poses many problems, in an environment where boundaries between departments are drawn in immovable stone. Modern drug research also requires an organized effort; an orchestrated team game in which individual interests may prove subservient to a larger goal. Paul Ehrlich knew what he was talking about when he said: 'Laboratory work is child's play in comparison; either a thing will go or it will not, and that is the end of it. But if you have to depend on hundreds of collaborators, and each of them believes that he can do better than any other, life really can be made rather difficult and bitter'.

Our successes in other 'mission mode' projects in the strategic R&D arena are sometimes held as models for the conduct of organized research, directed from the top. But it must be remembered that the commitment of resources and organizations to these programs have been substantial and the technical goals clearly defined. The construction of an atomic bomb or even the vastly more useful communications satellite require the implementation of tested designs and procedures. The true 'intellectual property' is already available. In the area of drug research the identification of targets and the methodology for attacking the enemy are much less well defined. There are also no visible institutions and personalities to champion major initiatives in this area. But the fact remains that we need to effectively combat the many threats to human health, particularly infectious disease caused by microbial pathogens in our surroundings. Some years ago Daniel Koshland, then editor of *Science*, highlighted the problem by emphasizing the fact that 'because of the capacity of microbes to adapt to new circumstances there will probably be a continuing battle for many years, a subterranean war in which complacency and lack of determination can result in pain and death' (*Science*, 1992, 257, 1021). There are many wars to be fought in the quest for the new therapeutics of the future. It is time that our agencies and institutions recognize the magnitude of the problem and the all-too-obvious limitations of our laboratories.

P. Balaram

