CURRENT SCIENCE

Volume 83 Number 9 10 November 2002

EDITORIAL

Drugs control: A slippery slope

Controversies surrounding the drugs and pharmaceuticals industry are not uncommon. The widespread and often, indiscriminate use of pharmaceuticals fuels a worldwide demand, which is serviced by a ruthlessly competitive industry. There is little doubt that nearly a century of pharmaceutical research has contributed spectacularly to improvement in human health and quality of life. Chemotherapy has its origins in the, now classic, work of Paul Ehrlich. The battle against bacterial infections was truly joined when Gerhard Domagk discovered 'prontosil', introducing the era of sulfonamide therapies. Alexander Fleming's, historic and serendipitous discovery of penicillin in 1929, was to be followed by the insights of Howard Florey and Ernest Chain and the exigencies of World War II, to herald the age of antibiotics. Rene Dubos' work at Rockefeller on gramicidin is sometimes overshadowed in popular histories of the discovery of antibiotics; the glamour of the penicillin story invariably proving irresistible. Drug research in its classic phase has been invested with an aura of romanticism, rarely associated with many other areas of science. Accidental discoveries which save human lives abound in the literature of classic medicinal and pharmaceutical chemistry. An interesting, relatively recent example is George Lesher's discovery of the antibacterial agent, nalidixic acid during a synthesis of the antimalarial, chloroquine. Serendipity, has been more often associated with drug discovery than rational, purposeful design.

A remarkable range of drugs, to combat infectious disease, control cardiovascular ailments, treat cancers and provide palliatives in the case of central nervous system disorders, have completely transformed the practice of medicine over the past half a century. Together with significant advances in diagnostics and vaccines, for the early and definitive detection of disease and the prevention of infection, the progress of drug research has contributed to the advancement of human health care in both the developed and developing countries of the world. But, the growth and increasing financial power of the major pharmaceutical companies, the escalating costs of drug research, rapidly changing business strategies and the growing complexities of international patent regimes, have brought in their wake many problems which merit careful analysis.

The recent controversy on the indiscriminate use of the drug nimesulide ('Nimulid') for treatment of pain and fever has focussed on the possible side effects, particularly the induction of liver complications in children. Nimesulide, a non-steroidal anti-inflammatory agent has rapidly become a 'best-seller', with estimated annual sales of over Rs 200 crores in India. Several Indian companies manufacture the drug, although multinationals have not yet marketed the drug in India. Interestingly, nimesulide competes with common drugs like paracetamol (acetaminophen), ibuprofen and aspirin for treatment of the most common of ailments, fever and pain. Critics of nimesulide point out that the drug was never approved by the US Food and Drug Administration (FDA); approval for use in the United States is often considered as the most stringent test that a new drug must pass. While, the drug was initially introduced in the 1980s in Italy, the European countries have recently been alert to possible complications following its use. In India, however, the use of nimesulide has been growing; doctors often tending to prescribe a drug, which is aggressively marketed. Since fever and pain are invariably treated by general medical practitioners or by self medication by patients, marketing strategies are likely to win over any rational assessment of efficacy versus toxicity, in a real clinical setting.

One of the harsh realities of routine medical practice in India is that for many medical practitioners, the sole source of information about the pharmaceuticals they prescribe are the ubiquitous sales representatives, who can be found hovering about in any neighbourhood clinic. Pharmacology and toxicology are not important subjects in the curriculum of medical courses; the continuing education of doctors, particularly the general practitioner, is not usually a matter of concern. The responsibility for ensuring, to the extent possible, the safety of widely used drugs rests with the Drugs Controller of India, whose office falls within the broad sphere of

responsibility of the Ministry of Health. Does the Drugs Controller's office have the necessary wherewithal to make scientifically valid decisions on drugs? In an area whose technical complexity grows with each passing day, can an office functioning under a ministry, not noted for its scientific strengths, efficiently and credibly discharge its mandate? Can an office steeped in a 'ministerial culture' resist the pulls and pressures of competing pharmaceutical houses? The present attack on nimesulide and the publicity given to reports of its liver toxicity in children must undoubtedly have its origins in the strategic marketing wars that drug companies are prone to wage. After all the literature reports on the adverse reactions of nimesulide and other non-steroidal antiinflammatory agents have been known for some time. If there was reason for concern it is incumbent on the Drugs Controller to make these public, rather than to respond only when the popular press raises the issue, stridently. It is also necessary for manufacturers of nimesulide, particularly those with the muscle of research and development departments behind them, to provide convincing data that toxicity in local populations is not significant. Interestingly, many of these questions would not have arisen if nimesulide was freely marketed in the United States, a country known for its stringent drugs approval procedures and a legal system which provides rapid redressal for wronged consumers.

The nimesulide story brings to mind one of the most famous tragedies of drug research, the introduction of thalidomide for use in controlling 'the symptoms of morning sickness and nausea in pregnancy', in Germany, Britain and several other countries in the late 1950s. The first dreadfully deformed babies were born in the 1960s, although a toxic effect in the users, peripheral neuritis, was detected much earlier. The drug was withdrawn only slowly, by which time the damage was widespread; there are some estimates that as many as 10,000 babies were born deformed. While the effect of thalidomide in causing human foetal abnormalities was clearly established, it is not clear if the use of animals to test the drug's teratogenic properties would have prevented its use. Once again the FDA had rejected the application to market thalidomide in the United States; an alert watchdog worrying about the drugs ability to induce peripheral neuritis. Despite its notoriety, thalidomide is back; new uses having been discovered for this old drug. For sometime, thalidomide has found use in treating inflammatory conditions, particularly in the case of leprosy patients with painful skin nodules. The ability of thalidomide to act as an immunomodulatory agent, its property of inhibiting cell movement and its capacity to hinder the growth of new blood vessels, angiogenesis, promise many new clinical applications, including in cancer and metabolic wasting, cachexia, seen in AIDS.

These remarkable properties of thalidomide, a deceptively simple chemical entity, appear to have allowed the drug to resurface. The drug has now been cleared for use in specific situations like leprosy and possibly, cancer, in India. Predictably, questions have been raised in the press on the wisdom of having a potent teratogen freely available on the shelves of pharmacies throughout the country. Pharmaceutical companies are reluctant to introduce drugs, whose potential markets do not ensure a significant turnover. The commercial motivation behind the introduction of new drugs (and old drugs for new applications) casts a shadow over the processes of drug regulation and prescription.

Regulatory issues in the area of drugs control will acquire a new dimension of complexity as biotechnology products, particularly recombinant protein pharmaceuticals become more widely used. The issues of quality and identity will be added to the problem of toxicity evaluation. Whether the Drugs Controller's office is equipped to address these increasingly difficult technical problems must be a matter of public concern.

P. Balaram