CURRENT SCIENCE

Volume 81 Number 4 25 August 2001

EDITORIAL

The ethical minefields of biomedical research

When Edward Jenner introduced the small pox vaccine he did not have to contend with an elaborate regulatory establishment. Pasteur's rabies vaccine and Ehrlich's chemotherapeutics also arrived in an era of limited controls. The exigencies of wartime saw penicillin reach the battlefield clinics in a remarkably short period. But over the years, particularly after the thalidomide tragedies of the 1960s, regulatory mechanisms for introducing new drugs for human use have become elaborate and expensive. In the United States, the Food and Drug Administration (FDA) acts as an alert watchdog, supervising the introduction of new pharmaceuticals after careful scrutiny of clinical trials, which are carried out in several phases. Indeed, the procedure by which a new drug wins approval for public use is long, arduous and costly. But for researchers in pharmaceutical laboratories the slow process of establishing clinical efficacy of a new drug can be a trying time. The growing controversy over the clinical trials carried out at the Regional Cancer Centre (RCC), Thiruvananthapuram, Kerala, of anticancer drugs, nor-dihydroguaiaretic acid (NDGA) and its tetra-*O*-methyl derivative (M4N) illustrates the cavalier attitude that prevails on the issues of international collaborations in biomedical research and the disregard for procedures when testing in human beings is undertaken. In this instance, a faculty member at Johns Hopkins University, Ru Chih Huang, appears to have made her own arrangements for clinical testing in India, without an ethical clearance from her University's Institutional Review Board. Johns Hopkins cannot, however, plead ignorance because the University has made payments for the trials to RCC. In India it appears that trials may have begun even before the formal approval of the Drugs Controller General's office. With the patients enrolled in the study coming from diverse educational and economic backgrounds, 'informed consent' for participating in the trial would hardly be meaningful. To further muddy the waters, the entire funding for the project in the US appears to have come from private sources; the involvement of a commercial organization invariably raises questions in such cases. While an enquiry has been instituted, it is clear that this incident should serve as a wake-up call to our biomedical establishment.

The real dangers involved in research with human subjects have been dramatically brought to the fore by the death of an apparently healthy volunteer, Ellen Roche, in a clinical study of asthma. This tragic incident, coincidentally at Johns Hopkins University, occurred following inhalation of hexamethonium bromide, a chemical that affects the nervous system, lowers blood pressure and relaxes airways. In the recent past a death has also occurred in a gene therapy trial intended to provide a means of treatment for an ornithine transcarbamylase deficiency. An editorial in *Lancet* (2001, **357**, 2067) points out that 'the whole idea of clinical trials is to ensure the safety of patients in general by confirming efficacy and safety of a treatment and by protecting them from exposure to unproven therapy'. In recognizing the dangers of bureaucratic overregulation, the *Lancet* essay concludes that 'fostering a culture of respect for the ethical conduct of trials should thus be part of any safety system'.

It is absolutely essential that a transparent, efficient and careful review mechanism for human trials be put in place by institutions, before clearances are sought from central authorities. At present, like most regulatory bodies, the Ethics committees in individual institutions and at ICMR lack credibility. They are also burdened by an inevitable sluggishness characteristic of most government bodies. Recent reports on trials of other 'cancer cures' on desperate patients, suggest that public perception of our ethics committees is far from encouraging. There is also an almost unrealistic eagerness for developing a clinically useful drug in many publicly funded laboratories, with only a limited appreciation of the long process of research and testing that is involved. Clinical trials in India pose another major ethical hazard. Very often the group of patients recruited for a study are hardly in a position to understand the uncertainties and risks of experimental treatments. It is therefore unsurprising that collaborative arrangements for human testing in India, of drugs and vaccines developed in the West are viewed with suspicion. It is

hard to avoid the legitimate fear, that poor and illiterate populations may be easily used to further foreign commercial interests. This fear is particularly justified when human clinical trials are not carried out in the country of origin of the drug, although this may not always be possible for diseases endemic only in the Third World. In these collaborations, the benefits, if any, may accrue largely to scientists and institutions. The biomedical research community therefore has a large public responsibility to ensure that it polices itself. At present the preoccupation of the Ministry of Social Justice and Welfare has been almost exclusively with regulation of experimentation on animals. Unfortunately, humans seem to have a lower priority.

But drug trials in humans is not the only ethical issue before the biomedical community. The dramatic advances that are taking place in the areas of stem cell research, xenotransplantation and gene therapies promise to throw up many new and difficult ethical questions. The rapidly transforming face of human genetics research, driven by the enormously powerful tools of genomics will pose several ethical conundrums. The treatment of many diseases of old age, Parkinson's disease amongst them, may benefit from embryonic neuron transplants. Clinical benefits have already been noted in patients, who are relatively young (Freed, C. R. *et al.*, *New Engl. J. Med.*, 2001, **344**, 710). Eventually, the use of human embryonic stem cells may power the next great advance in enhancing human health. But, the use of 'spare embryos' generated in the course of *in vitro* fertilization procedures finds many opponents, the world over. The growing crescendo of controversy over the issues of reproductive and therapeutic cloning is not likely to die down very soon. Clearly, the fruits of the breathtaking advances in modern biology can be savoured only after we have negotiated the ethical minefields of biomedical research.

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