DISCUSSION

Research on hire

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I recollect one of the first lectures in my first year of medical college where my venerable professor thundered: "... the first thing that a doctor should have is confidence. If you kill a patient, kill him with confidence." This is a classic expression of the necessity felt by the medical profession to maintain a veneer of confidence, even in the face of relative uncertainty.

In such a setting, medical technology is often used, not as a legitimate tool for diagnosis and treatment, but as a prop to hide inadequacies regarding knowledge about what constitutes the best course of action. In order to protect themselves from the anxieties which would otherwise accompany their relative ignorance, the profession seeks succour by immersing itself in the mindless pursuit of 'advanced' technology. The use of technology becomes an end in itself rather than a means to relieving human suffering. The last century has given us X-rays, ECGs, sonography, computerised scanning and much more. Yet, instead of clearing the prevailing chaos in medical practice, many of these tools have compounded the chaos. Not because it was inevitable, but because control over these technologies has been the driving force behind the immensely profitable health care industry. Patients are over-investigated, over diagnosed, over treated and under cared for because the practice of medicine has to play second fiddle to large corporate interests.

Contract research

Medical research is often organised, paid for, commissioned or subsidised by the drug industry. The companies commissioning such research are only looking for conclusions which will enable them to market their product and reap profits. Nowhere is this more apparent than in the manner in which medical research is conducted in the 'seat' of the pharmaceutical industry, the United States.

An estimated 2 million Americans got hooked on to Redux (dexfenfluramine), a new anti-obesity drug marketed in the US by Wyeth-Ayerst, after it was approved by the US FDA in April 1996. At its peak popularity, doctors were writing 85,000 new prescriptions a week. But a little more than a year after the drug's introduction, this craze collapsed, as patients began to exhibit symptoms of damage to their hearts and lungs. Fearing an epidemic, the FDA banned the drug in September 1997. (1) The manner in which 'scientific' evidence was created in favour of Redux is a shocking indictment of the system of medical research. In 1994, Wyeth had signed a $180,000 contract with a medical publishing company called Excerpta Medica that offered pharmaceutical companies an invaluable tool: ready-made scientific articles, placed in leading medical journals, and carrying the signature of influential academic leaders. Excerpta laid out for Wyeth a schedule of nine articles, each with a carefully crafted message aimed at a targeted audience, from primary care physicians to cardiologists to nurse practitioners to pharmacists. The articles had a 'writer' and an 'author' - but they weren't the same person. The writer was a free-lancer who was paid $5,000 to actually write the articles. The 'author' was often a top university scientist who was paid $1,500 to review the work and assign his or her name to it for publication.

The Redux story clearly focuses on the growing reliance of university scientists on corporate funding. Clinical research is now a multi-billion-dollar industry, with hundreds of testing and drug companies working with thousands of private doctors. Patients have become commodities, bought and traded by testing companies and doctors. The number of private doctors in research in the US since 1990 has almost tripled, and top recruiters can earn as much as $500,000 to $1 million a year. Reports of fraud in drug trials are pouring in. Such abuses point to weaknesses in the new system that has developed in recent years for testing experimental drugs. No longer does the pharmaceutical industry rely on career researchers at academic medical centres, whose professional reputations are forged on the quality of their data. Rather, the industry has turned to thousands of private-practice doctors for whom testing drugs is a sideline for making money.

Research in developing countries

Medical research in the developing world suffers from the problems of underdevelopment, on which are superimposed the ills of a neo-colonial approach assumed by external research funding. In the developing world, research is poorly funded, monitored and prioritised. The situation is compounded by foreign domination in setting research priorities. While, globally, medical research is fuelled by corporate interests; the market for medical technology and pharmaceuticals in the developing world is very small. The size of the Indian pharmaceutical market, for example, is less than one-tenth of the market in the US or Japan. As a consequence, donor-driven research in developing countries (largely, corporate sponsored research) focuses on areas of interest in their home countries. Tropical medicine (itself a colonial construct) has a long history of descriptive studies that benefit researchers but have no direct implications for participants. For example, a bibliography of research up to 1977 in Papua New Guinea identifies 135 publications that describe Melanesian blood groups but only 25 concerned with treating malaria (2). Different 'styles' of foreign donor driven research are prevalent. (3). 'Postal research' - where western researchers request colleagues in developing countries to courier to them biological samples. 'Parachute research' - where researchers travel to developing countries for short periods and take back biological samples. The most prevalent is the practice of maintaining 'annexed sites' for field research, led and managed by expatriate staff. These 'annexed sites' attract promising academics away from national institutions, and their research findings are infrequently translated into policy and practice. Research fellows in 'annexed sites' may receive good training there, but few return to national institutions. In a welcome development, India has recently forbidden 'annexed site' research and outsiders are now obliged to work through Indian institutions. However the long-term advantages of this move will, in all probability, be frittered away given the encouragement being provided to public sector R&D institutions to undertake contract research for corporate entities.

Drug companies have been known to perform research in developing countries that do not conform to the Declaration of Helsinki and could not be conducted in the developed world. Reasons quoted for conducting research in these countries, rather than developed countries, are lower costs, lower risk of litigation, less stringent ethical review, the availability of populations prepared to give unquestioning consent, anticipated under-reporting of side effects because of lower consumer awareness, the desire for personal advancement by participants, and the desire to create new markets for drugs. The commercial secrecy that surrounds early clinical research, and safety and dose ranging in phase I trials in paid normal volunteers (that is, poor volunteers), means that much preliminary research is unpublished, particularly when adverse effects are high and further development is abandoned. (3).

Medical research in India

There is, however, no denying that India (as a consequence of its size and ability to pledge greater funds) is different from most developing countries. Real science and research is done mostly with public money and mostly in non-profit institutions. But such indigenous research funding is still too small and too badly organised to address local priorities. A report published in 1997 in Current Science, a journal of the Indian Academy of Sciences, suggested that most medical research in India is unrelated to the country's major health problems. The report, based on an analysis of research publications from India indexed in the Medline database, said that achievements in research have 'little influence' on healthcare delivery. It lamented that research seemed to be concentrated in the fields of tertiary health care and new biology. (4)

There also exists a problem in defining local priorities. For long the two thrust areas for medical research in India have been vaccine research and research on contraceptive technologies (and recently, reproductive health). Both priorities can be contested on the ground that they emanate from a view of public health that is technocentric - vaccines as 'quick-fix' remedies for communicable diseases and contraception to control population growth. Given the hype surrounding both these concerns, government-funded research in these areas has scant regard for standard ethical guidelines.

Unethical and dubious

The decades of the 1980s and '90s have thrown up numerous instances of unethical and dubious research in the country. Research on long acting hormonal contraceptives like Net-En, Depo Provera and Norplant have been conducted without observing ethical requirements like informed consent and the need to follow up participants.

A team headed by Dr G PTalwar at the National Institute of Immunology (NII) persisted for years with trials to develop a contraceptive vaccine despite criticisms that these trials were being run unethically. The vaccine passed through phase II clinical trials in the late 1980s. Only 80% of the women who received the vaccine showed adequate response necessary for contraception. More importantly, according to published reports on the trial, only 94 out of 162 women in the trial 'volunteered' for long-term follow-up. The Indian government did not give approval for phase III clinical trials of the vaccine but continued to fund the research on contraceptive vaccines. The trials were put on 'cold storage' only when Dr GP Talwar retired from the NII. In 1998 it was revealed that the Institute for Cytology and Preventive Oncology, had left cervical dysplasia (a pre-cancerous condition) untreated in 1,100 women to study the progress of the disease, without warning them or taking their consent. In at least nine women the lesions progressed to invasive cancer, and 62 women developed localised carcinoma of the cervix before they were treated. The study had been sponsored by the Indian Council for Medical Research, whose function is to lay down the ethical guidelines for medical research. The investigators said, in their defence, that they did not obtain written consent because most of the women in the study were illiterate and also because written consent was not mandatory when the study was launched! (5)

In 1997 the scandal surrounding trials on quinacrine sterilisation forced the Supreme Court of India to step in. Quinacrine was used in the treatment of malaria till it was replaced by better drugs. Some time back there was renewed interest in its use in a method of 'chemical' sterilisation. In June 1994, the WHO Consultation on Female Sterilisation Methods categorically stated that human trials with quinacrine should be stopped forthwith pending the outcome of toxicological studies. In India, quinacrine sterilisation was carried out in the '90s with 'hundreds of doctors involved' according to an early convert to the cause, Dr.Biral Mullick. Coordinating the supply of drugs and equipment in the country was Dr.J.K.Jain, former MP. There were widespread protests against these trials. The Government of India denied granting approval. Finally, bowing to the public outcry, quinacrine sterilisations were banned by the Drug Technical Advisory Board in 1997. (6)

There is a discernible pattern in all the above instances. All of them pertain to research on contraceptive technologies, reproductive health and vaccine research. More importantly, all of them (except in the case of quinacrine sterilisation) have been conducted in public funded institutions using public money. They point to the extreme laxity in existing regulatory institutions and mechanisms and also to the tendency of such institutions to submit themselves to pressures when faced with so called 'national priorities'. Government sponsored (or approved) research in India, seems to have been fraught with equally potent dangers as corporate funded research is globally.

The anarchy in medical research in the country is typified in three recent examples, only one of which has received some publicity. The last pertains to a clinical trial conducted on human subjects in the Regional Cancer Centre (RCC) in Kerala, with an experimental drug in advanced oral and cervical malignancies. The trials were conducted in collaboration with the John Hopkins University in the US. The drug used, M4N, is an active principle of 'chaparral tea' made from leaves of the creosote bush, a common American desert plant. Although chaparral tea has been used over the years as an herbal remedy for cancer, it is also known for its toxic effect on the liver. While the trial was conducted in 1999 and 2000, the

application for permission to conduct the trials was forwarded to the Drug Controller of India only in February 2001! Further, the Ministry of Health and Welfare states that the RCC was granted permission to import M4N from Johns Hopkins only in February 2, 2001. Apart from these procedural problems it now appears that the trials ignored basic norms regarding informed consent. Further, a preliminary enquiry indicates that subjects enrolled in the trial were given the experimental drug in preference to established treatment regimes, a clear violation of the Declaration of Helsinki on research on human subjects. The trials had not been approved or reviewed by any of Johns Hopkins' institutional review boards concerned with the protection of human subjects, in spite of the Centre's claims that the permission for the trials were granted on the basis of 'pre-clinical and other relevant data'.

Even more bizarre is the report of a trial of another 'anti-cancer' cure conducted in Calcutta in 2000. The trial was conducted on 24 patients by a team comprising a private medical practitioner and a group of non-medical scientists at the Indian Association for the Cultivation of Science, (IACS), a non-clinical organisation. The results of the clinical trial have been published, of all places, in the Indian Journal of Physics! (7). The journal, coincidentally, is run by the IACS. The paper acknowledges that the trial was conducted through funding from the CSIR and DST and had the approval of the Institutional Ethics Committee of the IACS. Clearly approval was not obtained from any body that is authorised to give such approval. The paper goes on to exhort that, "We (authors) sincerely hope that researchers and clinicians with open minds will immediately make a concerted effort to use and to further improve the present formulation and treatment." Worse still, the main ingredient of the drug formulation is a chemical (methylglyoxal) purchased from the American warehouse supplier, Sigma Chemical Company, whose chemicals are laboratory grade, not intended to be used as drugs, i.e. not biological grade.

The third instance is the permission granted by the Ministry of Health and Family Welfare to conduct trials of the long-acting hormonal contraceptive, Netethisterone Enanthoate (NetEn), in 12 medical college hospitals across the country in 2001. The Ministry has not released any other details regarding the purpose of the trial or the protocols to be followed. It is being presumed that the trials are a prelude to introduction of NetEn in the country's population control programme. Various health and women's groups have represented to the National Human Rights Commission (NHRC) against conduct of the trials on the grounds that the introduction of NetEn in the mass population control programme is unacceptable given the drug's potential toxicity and the absence of a monitoring mechanism.

What informs medical practice?

There is possibly an even more fundamental conundrum that faces medical research in a country like India. Research output is, as yet, too insignificant and too unfocused to inform the practice of medicine in the country. The latter continues to be largely determined by medical research conducted in the West. This situation has been given a novel twist recently by Dr Samiran Nundy in a letter to the British Medical Journal. He argued that given the state of medical research in the country it made more sense to first attempt to regulate medical practice in the country rather than regulate medical research (8): "That medical research in developing countries is meagre and of generally poor quality is well known, and it has not improved in the past 20 years. Should one therefore discuss research ethics in developing countries when they barely exist? In my view the ethics of medical practice is more important. To see how the public can be safeguarded from an inefficient and often corrupt medical system and receive comprehensive health care of a reasonable quality is paramount."

Such issues arise today because the research institutions in the country have singularly failed to provide any cogent direction to the practice of medicine. It would almost appear as though the two work in entirely different paradigms. Unless there is, at the least, an attempt to marry research with practice, public perception of medical research will continue to range from suspicion to derision.

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