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Of Human Guinea Pigs

Preeti Mehra

Nearly 10 per cent of the women on whom the sub-dermal contraceptive Norplant was experimented cannot be traced. Did these women know that this device had been abandoned in the USA? Did anyone bother to get their informed consent of being experimented on? The ethics of medical experimentation demand that the interest of the subject should prevail over those of science and society. But the medical profession and pharmaceutical companies often ignore these principles, says Preeti Mehra.

The issue of the medical ethics of clinical trials on human beings has been highlighted once again with the Indian Council of Medical Research's own admission that 10 per cent of the women on whom trials of the new sub-dermal implant contraceptive, Norplant, were conducted have been lost to follow-up. This means that today there were any number of women in the country who have the two-rod contraceptive, Norplant 2, implanted in their upper or lower arm and are not aware of its hazardous properties. This is the same Norplant 2 which had been withdrawn from the US market because the manufacturers found it uneconomical to conduct additional studies on it after doubts were raised about the teratogenic and carcinogenic potential of the synthetic material, elastomer 385, that it contains.

In fact, the `health advocates' who met representatives of the ICMR in December last when this information was revealed, recommended that they "make every effort to located each and every woman who has the implant in her and remove the same expeditiously. Also, that the health of all subjects of this experiment (all phases) be monitored."

While the health risk to these subjects is, of course, of primary importance, so is the issue of ethics involved in human subjects as virtual guinea pigs. In fact, the ICMR's own policy statement on ethical considerations involved in research on human subjects states: "in view of the increasing research being carried out on human subjects and the ever widening complexities of medical research, guidelines for experimentation on human subjects in the country are required to make certain, as far as possible, that the rights and welfare of human subjects on whom experiments are carried out are adequately protected; that the risks to an individual are outweighed by potential benefits to him or to society or by the

importance of the knowledge to be gained; that informed consent is obtained from the individual by methods that are appropriate and adequate; that the clinical investigation on human subjects is carried out by an investigator who has the requisite background and competence to carry out such research; that the investigator has a framework for obtaining advice, support and assistance from his peers before embarking on a particular clinical research programme."

The policy statement goes on to mention: 'It is expected that the guidelines would protect volunteers and patients participating in clinical research from being exposed to unjustified hazards and risks during their involvement in the research project." It also states that the ethical committee should review every proposal for research on human subjects to assess among other considerations whether "... proper preparations would be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death."

In the case of Norplant 2, some of these guidelines seem to have been forgotten, for, a long-acting contraceptive naturally needs very close and extensive monitoring. It should have, in fact, been done on a stable population of medical personnel. The question that now arises is: who is responsible when subjects are lost to follow-up, or, in the case of drugs and other contraceptives, face side effects, injuries, physical or mental suffering?

While in India there has been no litigation regarding the issue, international guidelines have been formulated following disclosures of extreme unethical practices or disasters having actually taken place. Dr. Pritam Patnani, head of medical education, Glaxo Laboratories, honorary professor and head of the forensic department of Sion Hospital and a medico-legal expert, offers a historical outline. Says he: "During the post-World War II trials at Nuremberg, over 25 medical men were accused of having committted war crimes of a medical nature against involuntary human subjects. Seven were acquitted, nine imprisoned and the other nine done to death. Their 'advances' in medicine were termed as research in 'thanatology' - the science of death. After the trials, the Nuremberg Code was developed as an answer to the question of what constitutes valid, legal, moral and ethical experimentation. A code was also promulgated in 1964 by the World Medical Association called the Declaration of Helsinki. This was later amended in 1975."

Though extensive guidelines exist and pronouncements have periodically been made by tribunals, often medical experimentation on human subjects has misfired. The most well-documented example is the thalidomide disaster when this drug was introduced in West Germany in 1957. At that time it was regarded as a safe and useful medication, especially in the treatment of nausea during

pregnancy. However, in 1961, the West German government issued a statement warning pregnant women not to consume the drug as it was found to be associated with malformations that occurred in thousands of infants born to women who had been treated with the drug. Although the drug had not been released in America, two-and-a-half million tablets had been given to physicians so that they could carry out informal clinical trials.

As a result of the thalidomide tragedy, an amendment was passed to the US Pure Food and Drugs Law in 1962 setting out a series of formal steps to be taken when testing the safety and efficacy of a new drug for human use. However, there were other instances in the coming years - the Dalkon Shield, Depo-Porvera, DES etc. have all created controversies leading to their ban or restricted use.

While there is no doubt that medical experimentation has to continue, specially for fatal infections and diseases, it is essential to ensure that the dignity and rights of human subjects are not compromised. Going through the international guidelines there are several that very obviously enter the grey area when it comes to India. While some of them have been culture specific in the Indian context by the ICMR in its policy statement, there are others that have not been spelt out.

For instance, the most important guideline is regarding informed consent. In India, the signature of the person is not seen as enough to obtain informed consent. Every ethical review committee has to formulate its own procedure according to the kind of subjects chosen for the trial. However, this is not always done as volunteers are too few, specially after the screening is done.

Dr. Arun Bhatt, head of the medical department of Ciba Giegy, recounts his experience during clinical trials: "It is very difficult to get volunteers for clinical trials in India. No one comes forward for scientific tests due to fear of pain or the unknown. For Phase I trials medical students are the best volunteers as they have the background information of what is going to happen to them and they understand the terminology. Because we are not allowed to advertise, we sometimes have to look at people who are not healthy. So they have to undergo an AIDS check-up, a drug check-up, investigation of the kidney and liver, cardiograms etc. For Phase II trials patients for whom the compensation paid is less are most often used. Compensation generally depends upon the duration of the blood supply and how much inconvenience the test will mean to the human subject."

The guidelines, of course, specify that a subject should only be paid compensation and in no way should this be used as an inducement or incentive for the patient. But, given the unemployment and poverty in the country, the so-

called compensation will most often be seen as an inducement or incentive for the subject. Dr. Bhatt, in fact, admits that sometimes professional volunteers also come for the trials as they see this as easy income. However, he describes them as "not a good source." Dr. Anil Pilgaonkar, member of the managing committee of ACASH, Association for Consumers Action on Safety and Health, takes the compensation rule even further. He says: "The compensation should take into consideration damage or adverse outcome of intervention, withdrawal bleeding or whatever side effects. Are these compensated for by the investigators?"

Dr. Pilgaonkar is specially concerned about what are euphemistically called 'promotional trials' where companies supply the approved drug to doctors, encouraging them to prescribe it. Here, he points out, there is no effort to even take the informed consent of the patient, as the patient is unaware that the drug is being 'tried' on him or her. Says he, "There are any number of trials done by doctors in this way. I have not made a survey, but I am pretty certain that no informed consent is obtained from the patients. The doctor here violates the oath he or she takes as a medical person. The oath requires doctors not to allow any external influence to affect them, but they do get swayed by a company's promotional effort."

Another guideline that does not seem to stand to test is the requirement that the human subject on whom the experiment is being conducted should not be subordinate to the investigator. The ICMR policy statement fleshes this out by stating: 'the proposed participants in a clinical research should be made aware, by a person not in a position to influence the patient such as the physician but, for example, by a social worker, of the fact that a new drug or procedure is being evaluated.'

In most cases the patient in a medical college hospital (where trials are carried out) is so uninformed that he/she does not know the difference between a social worker or a doctor. And even if patients do, just being told that the doctor is going to give them the davai is enough because, in a sense, the doctor is viewed as God. For that matter, patients in government hospitals are subordinate to the medical persons concerned, as they do not have an alternative source of medical care due to the lack of enough government medical centres and the exorbitant prices of private medical care. Dr. Arun Bhatt does not contest this observation. He says, "Yes, there is a chance that the patient will act under obligation as he/she does not want to refuse the doctor anything. But our people refuse experimentation for other reasons out of their own conviction, like not wanting to give blood or the fear of pain."

He also recalls instances when informed consent has not been the norm. He gives the example of WHO clinical trials for river blindness in West Africa. "Here", he

informs, "no written consent was taken from individual community members. The importance of the clinical trial was explained to the village head and his informed consent was taken for the rest of the community."

A typical example of informed consent is vividly revealed in Deepa Dhanraj's latest documentary on family planning, Something Like A War. She documents how women are informed about the contraceptive during a trial. All they are told is, "Is ko laga lo to bacche nahin hongen. Is se kuch nahin hoga." (Use this and you will not have children. It will not harm you). She also interviews two Norplant human subjects who come on record saying that they were not told it was a trial being conducted on them. Another survey by women's organisations in Hyderabad on Net-En, the injectable contraceptive, revealed that the women were merely told, "Yeh injection loge to bacche nahin hongen (If you take this injection, you will not have children)." No side effects were explained.

Among the major guidelines regarding human experimentation is the formation of a medical ethics committee in all medical colleges and research centres, which should have on it an expert on drugs and one or two non-medical persons who could provide guidance to the committee in the matter of ethics and law. While these committees do exist, they are not considered ideal even by those who conduct clinical trials. Dr. Bhatt opines, "I am not sure if ethics committees existing today have the ideal combination of people. Only then can you protect the human rights of the individual. There is definitely scope for improvement where ethics committees are concerned. It has happened sometimes that because an ethical committee does not meet to approve of a clinical trial we have to withdraw the study from the hospital." Dr. Pilgaonkar asks another question: "Why are clinical trials and ethical committees kept under so much secrecy? What is secretive about trying a drug for future use? Ethical committees should be made public, the human subjects specifically should know the committee members and feel free to approach them if there is a problem. This could serve as a redressal system for the human subjects and would endorse the spirit behind scientific experimentation on human beings."

Referring to the spirit behind human experimentation once again, Dr. Pilgaonkar emphasises the two important principles in the Declaration of Helsinki: One, that the interest of the subject prevails over the interest of science and society and, two, that no biomedical research can be undertaken unless informed consent is obtained. He feels that these principles are quite often not observed. His fear is that the extent of information that should be given to a subject is not given, nor is the competence of the subject ascertained to understand, appreciate and reflect the issues involved in the experimentation.

An excerpt in the book, Human Experimentation and Medical Ethics, a report of the XVth Council For International Organisations of Medical Sciences' round table conference in 1981 echoes the same kind of sentiment. It recounts a report from Nigeria regarding the freedom to withdraw consent: "Our personal experience is that provision of drugs, money and food are the essential prerequisites for patient retrieval in clinical research. Not a few of our research patients or volunteers become so dependent on this apparent kindness that withdrawal from the study programme becomes unthinkable - yet, we are often aware of the patient's disenchantment with the study. It is, therefore, hypocritical to pretend the highest ethics merely by informing a peer review committee that participants in a study were clearly informed that they could withdraw from the study."

On the subject of withdrawals or what are called drop-outs, Dr.Bhatt informs: "The longer the follow-up, the more chance there is of drop-out. Trial patients often drop to 10 per cent of what you started out with. Then, the question is of the motivation of the investigator." Dr. Pilgaonkar who belongs to a consumer action group bemoans just this kind of thing. He says, "If there is a drop-out, the onus should be on the investigator, particularly where repercussions of the experiment are long-term - like in the case of Norplant. If the investigator is not sure of follow-up, such experiments should not be done. But generally, the medical community does not have this kind of sensitivity. Take the case of the glycerol tragedy at J J Hospital, Bombay. While Justice Lentin gave an excellent judgement and his report clearly stated that the victims of the tragedy suffered kidney damage, no one has till date bothered about those patients who were given glycerol and are still alive. Justice Lentin's mandate was only to investigate the deaths, but the medical fraternity could have easily taken out the list of people who had been administered glycerol and followed up their condition. They too could have suffered kidney damage."

In fact, in the medico-legal aspect of human experimentation there is a special section on negligence. Dr. Patnani outlines it: "Negligence is a tort or civil wrong and is defined: 'If one person acts without reasonable care towards another person, to whom he owes a duty of taking such care, and if a damage thereby is caused to that person, an action in the court of law may result in damages being awarded for the injury.' In the event of any death occuring, the element of criminality will be looked into." Therefore, negligence, even indifference, can be legally dealt with.

The last but most important aspect of ethics in human experimentation is with regard to developed countries conducting clinical trials in developing countries. While they argue that to introduce the drug into the developing country it is essential to conduct trials there, there are certain implications which need careful

preliminary assessment. The international code outlines these as: 'The investigation may subserve external rather than local interests; foreign investigators and sponsors may not possess adequate insight into local mores, customs and legal systems; the absence of any long-term commitment to subjects involved in the research, and withdrawal of out-posted personnel on completion of their task, may result in local disillusionment; lack of accountability may deprive subjects of any form of compensation for incidental injury.' Therefore, the code recommends that, wherever feasible, externally sponsored research should be undertaken through an established local institution and some tangible commitment in terms of service and training.

However, despite these extensive guidelines and medico-legal regulations, human beings continue to be treated as guinea pigs for the medical community and pharmaceutical companies. Even highly-placed doctors, who obviously do not want to be quoted, admit that many of the guidelines are merely on paper, that ethical committees function only to fit a requirement and often slum and other deprived populations are used for experimentation purposes. And, unless public vigilance committees comprising of informed and concerned people are not formed, the indifference will continue - a man will have a drug side effect and keep silent, a woman will harbour a hazardous implant in her body and not realise its adverse repercussion.