The Medical Ethics of Clinical Therapeutic Trials*

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SUMMARY

The pharmaceutical industry is continuously providing the doctor with new potent drugs for his armamentarium, to be used in the endless battle against disease. The basic requirements for a good drug is efficacy combined with a wide safety margin. To be able to establish this, the new chemical substances must be tested in man. As clinical investigators of new substances, we have a moral obligation towards patients and humanity to conduct these investigations on a sound scientific basis, taking heed not to violate the rights and privacy of man. A personal ethical conscience is the prime prerequisite for conducting clinical therapeutic trials.

S. Afr. Med. J., **47**, 18 (1973).

The conducting of clinical therapeutic trials is today considered as a separate speciality of medicine, although not universally recognized as such. Clinical therapeutic trials, or human experimentation with drugs, are absolutely necessary, because data gained from experiments on animals cannot always be directly extrapolated onto man as being applicable.

Variations are also found in the different animal species. It is impossible to obtain data in animals regarding drug allergy, drug idiosyncrasy and drug intolerance. Also, the Drug Control Councils of countries, by law, require proof that a specific drug must be tested in humans to prove its efficacy and safety. If the human data cannot be provided to the satisfaction of a particular Drug Control Council, the manufacturer will not be allowed to release the drug on the open market; consequently a drug which may have been of great benefit to humanity, will be lost. The very fact that the Drug Control Councils require human data, is a safeguard for patients and doctors. This requirement of human data, gained through clinical therapeutic trials, prohibits to a very large extent the marketing of useless and unsafe drugs on which the public would have spent their money, and maybe even have risked their lives.

Because of the rapid advance in the development of pharmacology and clinical pharmacology in the past 50 years or so, the world was faced with what might be termed a 'chemotherapeutic revolution'. Potent life-saving drugs were discovered in close succession, and the world needed a control of some sort with regard to this revolution. Critical analysis of data of clinical therapeutic trials done in the past showed shortfalls and large gaps, and these studies were rejected because of the lack of unbiased scientific value. Some drug trials were, and unfortunately still are, just personal testimonials from the investigators. This unreliable and therefore unsatisfactory practice led to the development of a specific methodology of clinical therapeutic trials. Soon the terminology of the methodology included terms such as placebos, controlled studies, comparative studies, pilot studies, single-blind studies, double-blind studies, double-blind cross-over studies, statistical significance, standard deviation and control groups. The naïve concept of 'poison or non-poison' is no longer acceptable. Zbinden[1] compiled a classification in 1963 of clinical toxicity, listing 15 categories necessary for clinical evaluation (Table I). The development of the methodology therefore soon placed an additional burden on the shoulders of the investigator or trialist in respect of the ethical considerations, when designing a clinical therapeutic trial.

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TABLE I. DRUG-RELATED TOXIC MANIFESTATIONS IN HUMANS[1] (ORDER OF CLINICAL EVALUATION)

I. Clinical pharmacology phase
1. Related to desired pharmacologic, biochemical, or endocrine effects; exaggerated effect at recommended dose.
2. Related to desired pharmacologic, biochemical, or endocrine effects; drug acting on wrong target organ.
3. Related to undesired pharmacologic, biochemical, or endocrine effects.
4. Related to tissue irritation and damage on direct contact (topical and parenteral agents only).

II. Controlled evaluation phase
1. Related to desired pharmacologic, biochemical, or endocrine effects, requiring pre-existing pathology which is not drug-related.
2. Related to desired pharmacologic, biochemical, or endocrine effects, requiring contributing exogenous factors.
3. Related to undesired pharmacologic, biochemical, or endocrine effects, requiring pre-existing pathology which is not drug-related.
4. Related to undesired pharmacologic, biochemical, or endocrine effects, requiring contributing iatrogenic and other exogenous factors.
5. Related to interference with absorption of nutrients.
6. Related to interference with natural defence mechanisms.
7. Related to tissue storage or precipitation of drugs or metabolites.
8. Toxic effects on the foetus.

III. Broad trial phase
1. Related to sensitization and allergic reactions.
2. Related to sensitization and allergic reactions requiring contributing exogenous factors.
3. Related to idiosyncrasy and other unknown mechanisms.

Claude Bernard is generally regarded as the father and founder of experimental medicine. Dealing with the moral and ethical aspects of human experimentation, Bernard states in his book *Introduction à l'Etude de la Médecine Expérimentale* that the principle of medical morality consists, then, in never performing in man an experiment which could be harmful to him in any degree whatsoever, though the results may be of great interest to science—that is, of benefit to save the health of others.[2] An uncountable number of human experiments have been conducted since Bernard postulated his principle of medical ethics. Hundreds, and maybe even thousands, of these studies were in direct conflict with the principle laid down by Bernard. It is unfortunately so, that the growing extent of human experimentation led to the abuse of the trust the patients put in the doctor. Medicine cannot advance without investigations on human beings. Claude Bernard accepted this and he merely asked *how*, rather than *why*, it should be undertaken.

The most pertinent example of our time of the abuse of the trust of the patient in the doctor, is undoubtedly the human experimentation done by the Nazi physicians. The methodology of the 'medical research' that was performed, shocked the world. The Nuremberg Trial focused the opinion of the public on medical research. On 2 June 1948, four physicians were hanged because they conducted clinical experimentation in a manner which was considered to be appropriate and acceptable to the world. After the trial which lasted 139 days, the United States Military Tribunal Number 1, rendered a 10-point code for permissible human experimentation, essentially summarizing the means to be employed for protecting subjects and assuring responsible research. A symposium on human experimentation, held 5 years later in 1951 at the University of California, accepted this code as a safeguard for the research worker,[3] and as a standard for medico-legal reference.[4]

The World Medical Association[5] in 1962, defined an experiment on a human being as 'an act whereby the investigator deliberately changes the internal or external environment in order to observe the effects of such a change'. Various codes of conduct for human experimentation have been postulated by various bodies and eminent individuals. Of the more recent codes the Nuremberg Code (1947), the code of the Judicial Council of the American Medical Association (1946), and the code of the Ethical Committee of the World Medical Association (Declaration of Helsinki, June 1964) are the best known. The Declaration of Helsinki recognizes a fundamental distinction in the fields of clinical research between studies with a direct diagnostic or therapeutic relevance to the individual patient, and research projects carried out to advance knowledge, but from which the subject cannot be expected to receive any direct personal benefit.

The Judicial Code of the American Medical Association[6] laid down only three requirements for human experimentation, to conform to its medical ethics. They are (*i*) the voluntary consent of the person on whom the experiment is to be performed must be obtained; (*ii*) the danger of each experiment must have been previously investigated by animal experimentation; and (*iii*) the experiment must be performed under proper medical protection and management.

Gellhorn[7] proposed a procedure for the decisions based on 6 main points:

1. Work should be carried out only with the hope of improving the patient's condition.
2. There should be a reasonable prospect of success based on animal and other work.
3. A protocol for control work and safeguard should be drawn up.
4. The proposed research programme should be reviewed by the worker's peers who are knowledgeable in the particular field.
5. The results should be systematically collected and analysed by independent observers.
6. The patient's written consent should be obtained before any procedure is undertaken.

Gellhorn believes that truly informed consent is impossible. He nevertheless believes that consent would give the patient his rightful status as a person, and not merely as an experimental being.

Clinical therapeutic trials can be broadly divided into two categories, viz: early phase and later phase studies. In the *early phase studies* the main aim, and very often the only aim, is to obtain basic scientific data on the pharmacological effect, and if possible on the pharmacodynamics and pharmacokinetics of the drug tested. For the investigator doing an early phase study the primary emphasis is therefore on basic research.

In *later phase studies* the main object is to accumulate data on the therapeutic value of the drug, optimum dosage, efficacy and side-effects of a drug tested in a large number of patients. In this type of study the investigator is primarily concerned with the patient as a patient. The well-known aspect of the doctor-patient relationship is therefore strongly in the foreground, as opposed to the early phase studies. Viewed in another way, in medical practice the patients seek the physician (later phase studies), while in research (early phase studies) patients are sought and selected by the physician (investigator).

The trial population participating in controlled therapeutic trials, can similarly be broadly classified into two categories, viz; those who stand no chance to benefit therapeutically from the experiment, and those who stand a very good chance to benefit therapeutically from the study. The trial population who will not directly benefit therapeutically from the investigation, may again be subdivided into healthy volunteers and patient volunteers.

When a study is conducted using volunteers, it is of prime importance that informed consent is obtained. Whether the consent is written or not, is a legal rather than a moral issue. What is of importance, however, is that the volunteer be fully informed as to what the study embraces. There is no right to withhold from a prospective volunteer any fact which may influence his decision.[7] Only true consent is of any value. By true consent is meant 'consent freely given with proper

understanding of the nature and consequences of what is proposed'.[9] Unfortunately we are not always able to execute the above requirements to the last letter, because a very large proportion of our population in Southern Africa is illiterate. Interpretations and translations by a third person to the patients are also not satisfactory, because it is known that the majority of the patients will fail to grasp the full meaning of the message conveyed to them. Despite this practical problem with which we are often confronted, we are compelled to explain to the patient what the study entails. The investigator has no right of persuasion, and facts should not be deliberately distorted. The patient must always be informed, that he may at any time during the investigation withdraw from the trial. In obtaining voluntary consent, although it may not be fully understood by the patient, the investigator realizes and acknowledges the right of the patient as a human being, and not merely as a subject of experimentation.

Goldstein[10] suggests that the patient should be told the following:

(i) a new drug has been developed that might be beneficial to him;

(ii) it can only be tested properly in a controlled way, so that some patients will receive the drug, while others will receive a different treatment;

(iii) the assignment will be made by chance;

(iv) certain risks are likely; and

(v) other unanticipated risks may materialize.

It is impossible to construct a formal ethical code that will embrace every circumstance that may be encountered during clinical therapeutic trials. Patients are still human beings and because of the complexity and variability of the human being, as well as the ever present individualism, it is unrealistic to subject them to a blanket formula. Each patient and each trial procedure should be individually judged. Should any question arise as to whether a certain trial or procedure is ethical or not, the investigator should first analyse his own motives and then refer to the guide-lines laid down by the various authorities. If uncertainty still prevails, he must consult his peers, who should in no way be attached to the proposed study. Final judgement on extremely delicate situations should only be made by an arbitrary panel consisting of doctors, scientists and responsible laymen. The emphasis of the judgement should be placed on how the investigator intends conducting the trial, rather than on what he intends investigating.

The greatest ethical challenge to the physician investigator, is preserving the delicate balance between individual risk and the common good.[11] Irrespective of what one's religious views are, I believe that the Golden Rule (Matthew 7 : 12), which states 'Whatsoever ye would that men should do to you, do ye even so to them' encapsulates everything that we understand under ethics. It is in fact the crux of the matter because 'the cannon of ethics of all communal living emanated from the Golden Rule'.[12]

CONCLUSION

Although various codes and guide-lines are available with which the investigator can familiarize himself and which he can use when conducting a clinical therapeutic trial, the ultimate decisions, judgements and *modus operandi*, rest in the hands of each individual investigator.

It is therefore essential that every investigator has at least a personal code which obviously must, to some extent, be compatible with that laid down by the various authoritative bodies. He should therefore develop an ethical conscience, which will not allow him to conduct a study in such a way that he will be ashamed to have it judged by his scientific colleagues, or by a responsible group of laymen and scientists. It is his ethical duty to do a trial efficiently. According to Glaser[13] 'The investigator's competence is a most important prerequisite'. Under competence is included medical skill, ethical competence and integrity.

The integrity of an investigation is based on the experimenter's ability to deal as honestly with consequences as he tries to deal with the experimental data and design.[14] De Bakey states that 'obedience to an ethical code is properly exacted by rigid, formal laws or injunctions, but is prompted by integrity, humanitarianism and benevolence, qualities that every physician should possess'.[12]

At present, and I believe for quite some time still to come, there is no alternative or substitute for man, in the investigation of a new chemical substance, with the ultimate aim of releasing this new substance on the market. Safety and efficacy are the main prerequisites of any drug, and to be able to establish these characteristics, the substance must be tested in man. It is for man's own good. The Drug Control Councils of the various countries are continuously requiring more and more information and data related to human experimentation before allowing registration, for marketing purposes, of a new substance. This is praiseworthy, but care must be taken not to increase these requirements to such an extent that it is no longer ethically justifiable. Doctors are also increasing their standards of critical analysis of trials done with drugs. This trend is also praiseworthy, but here again we must take heed not to be hypercritical. If the drug-regulating bodies and the medical profession become hypercritical in their analysis, the time will come when legislation and laws, as opposed to our present guide-lines, will be enforced to regulate the methodology of clinical therapeutic trials. The execution of unscientific and unethical clinical therapeutic trials must be avoided, as far as humanly possible. Legislation and laws are not the ideal way to accomplish this.

Abrams *et al*,[15] expressed their views as follows: 'Experience has indeed brought complexity and sophistication, and thus, we are disturbed by the recent trend which shifts the decision as to whether a new drug should be used or not away from the investigators primarily concerned, to hospital committees and government agencies. There should be no incompatibility between the equally honourable objectives of delivering

to the public important new medicines *and* reasonable safety'.

The investigation of new substances in man should only be entrusted to investigators who are competent, in the broadest sense. It will be their privilege to conduct these early phase studies, because they realize and appreciate the heavy responsibility that accompanies this privilege. Unless an investigator has an acceptable ethical conscience, he should not be given the opportunity to do clinical trials.

It is a truism that the research of today is the routine of tomorrow. It is therefore entirely in our hands, as investigators, to conduct controlled clinical therapeutic trials in such a way that it does not lead to unwise legislation in a field where reliance must be placed on competent human judgement.

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