Medical experimentation : International rules and practice

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In this paper Professor Deutsch, a specialist in medicolegal matters, traces the development of rules about medical experiments and considers the origin of ethics committees. The Cartwright Report conclusions on these matters are also discussed.

I. MEDICAL EXPERIMENTATION : DEFINITION AND TYPES OF EXPERIMENTS

A. Definition

Experimentation has to be distinguished from treatment. Treatment is never to be regarded as experimental solely because doctor and patient are not sure about the success. Medical treatment concerns the person, a complex being, so that expectations cannot be absolute. The medical trial therefore is not the opposite of success, but has to be contrasted with standard treatment. Standard treatment is any medical measure that is commonly used by physicians and specialists in treating the particular illness. By contrast the trial or experimentation concerns a medical intervention that aims to lead to a new standard of treatment. Treatment here is used in the broadest sense; it is not just treatment in the true meaning of the word, but encompasses diagnosis and pre-emptive matters as well such as inoculation and disinfection. Research, trial and experimentation are used to describe the same phenomenon. There can be treatment and trial working together in the same medical measure. Sometimes both are of equal importance; sometimes it is necessary to know whether the emphasis is on treatment or experimentation.[1] There is still a question mark as to whether the principal investigator or the single investigator can undertake the trial only if he has some objective criteria or if he has the subjective belief that the trial will be of advantage to the patients and for science. Probably there have to be a few objective criteria on the one hand and some

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1 In the German Supreme Court case BGHZ 20, 61 the court distinguished between whether the medical measure looks towards the restoration of the health of the patient or looks more towards the research purposes. The *Report of the Cervical Cancer Inquiry* (Government Printer, Wellington 1988) ("The Cartwright Report") seems to be ambivalent in this respect; on p63 the question just is "whether it had a research component". On p69 suddenly "the principle of primacy of aim" becomes important.

kind of subjective belief in the superiority of the new method on the other. There is an old English case and a recent American one that show the range of experimentation.

Slater v *Baker & Stapleton* [2] : The patient brought an action upon the case against a surgeon and an apothecary. They were employed to cure the broken leg of the plaintiff. The defendants broke and disunited the callous of the plaintiff's leg after it was set. The court gave judgment for the plaintiff. It was possible that the surgeon had wanted to try out a new medical instrument. But it is not permitted to break an already broken, but set, bone again without the consent of the patient.

Carmichael v *Reitz* [3] : The plaintiff had suffered pulmonary embolisms and thrombophlebitis after taking Enovid. During the proceedings another doctor tried, for purposes of proof, Enovid on the patient again. The same symptoms as before appeared. The patient then sued for damages in this respect too. As far as the test was concerned the court gave judgment for the defendant company. The plaintiff had acted at her own peril.

B. Types of experimentation

There are two basic types of experiments: the therapeutical trial and purely scientific research. Therapeutical work is experimentation if it is used for the purpose of furthering the health of the experimental subject. The purely scientific experiment does not in any way improve the health of the experimental subject. As far as therapeutical research is concerned there is the distinct possibility to weigh the advantages against the risks for the patient concerned. With scientific experimentation it is very hard to compare the advantage for the public with the risk for the subject. Hence in this field just minimal dangers are accepted.

A controlled clinical trial is a medical undertaking that is done with regard to a certain result and which is watched in this respect. Usually at least two groups of experimental subjects are formed: The test group and the control group. The test group gets the new treatment; the control group receives the standard therapy or, in minor matters, gets a placebo, which means that it is not treated at all. Placebo controlled clinical trials are commonplace in matters of sleep disorders and pain-relief. In serious matters placebo controlled experiments can be conducted only where there is no effective standard treatment. Sometimes there is more than just one test group. The trial is blind if the patient or the experimental subject does not know whether he or she belongs to the test group or the control group. The research is double blind if the doctor, who is treating the patient, is in the dark as well. Sometimes even the principal investigator does not know who belongs to which group. There is crossover, if during the trial the subjects are moved from one group to the other. To get a statistically valid result it is usually necessary to randomize the patients or experimental subjects.

Randomization is there to counteract artificial results. Randomization particularly works to discourage persons with identical backgrounds from entering just one group.

2 (1767) 2 Wils KB 359; 95 ER 860.
3 17 Cal App 3d 958 (1971).

Usually randomization follows special rules established by clinical statistics. The types of experimentation can be gathered by the following two cases.

Karp v *Cooly* [4] : The widow of a dead patient sued the famous heart surgeon Cooly. With the written consent of the patient Cooly had tried to save the critically ill patient. After unsuccessful open-heart surgery Cooly removed the heart and installed instead a pump that had been used in dogs only and not been tried out on human beings. A few days later the artificial heart was taken out and a transplant put in. One day later the patient died of renal failure. The court gave judgment for the defendant. There had been no negligence on the part of the surgeon. Moreover the patient had knowingly agreed even to the use of an artificial heart.

"Rice and Beri-Beri, Preliminary Report of an experiment conducted at the Kuala-Lumpur Lunatic Asylum"[5] : In a psychiatric institution in Kuala Lumpur the chief of service divided his inmates into two groups. One group was given uncured rice and the other got white rice. From the 120 inmates who lived on the cured rice 34 developed Beri-Beri and 18 died. The group that ate only uncured rice consisted of 123 patients. Just two developed Beri-Beri, but perhaps had developed it before they had become inmates of the asylum. The trial established once and for all that Beri-Beri is an illness that is based on deprivation of vitamins.

C. Typical contents of a research protocol

A controlled clinical study is undertaken on the basis of a research protocol. The research protocol is itself based on the following statements : At the outset there is an outline of the standard of science today, followed by the question raised by the research protocol, this itself followed by the result of a possible pilot study and finally the expected result. The research protocol then usually goes on to name the criteria for inclusion and exclusion of subjects and the whole system of selecting subjects. It is necessary to make a statement concerning the overall number of experimental subjects and the anticipated reasons for abandoning the trial early. If it is not expressly stated the study is assumed to be discontinued if one of the original elements has changed considerably. Moreover the overall set-up of the study has to be disclosed. If it is a multi-centre study all the participating institutions and doctors have to be named. This is even more important if it is an international study. The information given to the subjects and their consent has to be documented. In some countries such as Germany compulsory accident insurance has to be arranged in the case of testing of pharmaceuticals. In some countries the government has to give its approval or at least be notified before the trial is started. Normally an ethics committee has to review the research protocol and to accept it or at least not object to it. Often special rules for the termination of the study are adopted. In longer studies, especially in multi-centre or multi-national studies a special committee is established with jurisdiction over the study as far as the prolongation or the termination of the study is concerned. The position of the principal investigators has to be determined. Most important is the part about the risks, benefits and expectations of the study. Here the work of the ethics committee

4 493 F2d 408 (US Court of Appeals 1974).
5 The Lancet, 26 June 1907, I, 1776 ff.

starts; even the consenting patient should not be put at an unreasonable risk that outweighs the possible benefits for himself or other patients. This is for instance the case if a chronically ill patient is to undergo a prolonged wash-out period before the trial starts or if in phase IV - studies the trial is undertaken for marketing purposes in the first place.

II. INTERNATIONAL LEGAL AND ETHICAL INSTRUMENTS

A. The starting point : The Prussian directive of 1900

There are no international treaties concerning clinical trials. Development has not been going that way. Medical experimentation is regulated typically by instruments whose legal qualifications are sometimes in doubt. But it has been the development over this century that experimentation is regulated mostly by national or international directives.[6] The first regulation on a national basis we know of was issued on 29 December 1900 in Berlin. The Prussian Minister for Health directed the university clinics to conduct experimentation only with patients after having obtained their informed consent. Experimentation with incompetent patients or children was not allowed. All experimentation had to be approved by the heads of the department.[7] This directive was due mostly to a public scandal created by articles in illustrated papers of the time. These concerned, among others, trials in German university clinics at the end of the 19th century with patients in the final stages suffering of venereal diseases without obtaining their informed consent. Since the publications in the popular press found their counterpart in scientific journals there was no use denying them.[8]

There is an interesting similarity between the first scandal concerning human experimentation at the turn of the century in Germany and the article by Coney and Bunkle entitled "An 'Unfortunate Experiment' at National Women's".[9] On both occasions the publications in widely read illustrated papers forced the authorities to react. In Prussia there was no use denying, therefore the directive came into being. In New Zealand the Cervical Cancer Inquiry was opened. A short time after the publication of the "Metro" article Prime Minister Lange announced that there would be a very rapid inquiry headed by a lay woman.[10]

6 As a result of the Cervical Cancer Inquiry in New Zealand Sandra Coney has suggested "the doctor's code, the Helsinki code, should be law" (*The Unfortunate Experiment* (Penguin, Auckland,1988) 258).

7 Anweisung an die Vorsteher der Kliniken usw. vom 29.12.1900, Centralblatt der gesamten Unterrichtsverwaltung in Preußen 1901, p 188f. Cf also v Bar, Medizinische Forschung und Strafrecht (Festgabe Regelsberger 1901, 230).

8 Cf Vikanty Veressayev (= v Smidovich): "The confessions of a physician" (1904) 332ff.; excerpts in Katz *Experimentation with Human Beings : The Authority of the Investigator* (Russell Sage, New York, 1972) 284ff.

9 "Metro" Auckland, June 1987.

10 Coney *The Unfortunate Experiment* above n6, 74. The reporter who had written the article went on to tell us "I suggested Silvia Cartwright, an Auckland Family Court Judge".

B. The 10 points of Nuremberg

In 1947 an American military tribunal sitting in Nuremberg and composed of three state judges issued their verdict in the so-called Medical Case.[11] The judgment rested on 10 points which the court used to distinguish between lawful and unlawful experimentation. The 10 points apparently originated with the court, but in reality probably were formulated mostly by the medical adviser to the prosecution, Leo Alexander.[12] Unfortunately because the 10 points were not discussed in open court some of them later seemed not to stand up to criticism. Therefore in the fifties an American committee proposed to change no less than 5 of the 10 points of Nuremberg.[13]

The Nuremberg Code followed the Anglo-American approach of valuing the will before the interest of the patient. Therefore it stated categorically that experimentation has to be performed with the informed consent of the experimental subject. Moreover the experimental subject has to have capacity, a rule which seemed to rule out experimentation on mentally ill patients or children. Very valuable is the rule concerning the right of the patient to drop out of the experimentation at any time. Today the right to withdraw the consent is not bound to specific reasons as in the Nuremberg code; the experimental subject can drop out anytime without giving reasons. Then there was the equally valuable ban against experimentation that somehow could result in major injury or death of the experimental subject. Less fortunate was the basis of the 10 points of Nuremberg in just addressing purely scientific experimentation. One rule has even been described as bizarre.[14] It is No. 5 where the experimentor is allowed to take a greater risk if he is participating in the study. Nowadays we know, that particularly high risks are often run by the principal investigator only. If he steps in often there is more risk than the average experimental subject would tolerate. Nowadays the 10 points of Nuremberg seem to have been superseded by the two Helsinki Declarations issued by the World Medical Association.

United States v *Rose* [15] : Professor Rose had furnished doctors at concentration camps with typhus vaccines. At the concentration camp of Buchenwald there were two groups treated. One group had been inoculated against the disease, the other was not. There were in all 729 experimental subjects of whom at least 154 died. If the inmates had been given information at all, they had been told that the experimentation was harmless and they would get better rations. Professor Rose was convicted because of

11 *United States* v *Rose,* Trial of war criminals before the Nuremberg Military Tribunals volume 1, 2 "The medical case" (1949). Cf Alexander "Medical science under dictatorship" (1949) 241 New England Journal of Medicine 43.

12 Alexander "Methods and Processes for Investigation of Drugs" (1970) 169 Annales of the New York Academy of Science 344; Deutsch, Die 10 Punkte von Nürnberg, Festschrift für Wasserman (1985) 69.

13 Ladiner-Newman, Clinical Investigation in Medicine (1963) 140ff. For criticism of the 10 points of Nuremberg see Moore "Therapeutic Innovation: Ethical Boundaries in the Initial Clinical Trials of New Drugs and Surgical Procedures" (1969) 98 Daedalus 502, 515.

14 Beecher *Research and the Individual* (1970) 234.

15 Above n11, Vol. 2 p264.

war crimes and crimes against humanity. Since he had openly criticized the experimentation this was taken as proof that he knew about the illegality of the procedure.

Halushka v *University of Saskatchewan* [16]: Halushka was a student who for a fee of $50 had agreed to act as a research subject at the university hospital. He had been told that a new pharmaceutical was to be tried out on him and that a catheter would be inserted into his vein. He had signed a general declaration that he had been informed and he had signed away all responsibility of the university and the physicians. During the trial a new anaesthetic agent "Fluoromar" was used and the catheter was even advanced towards his heart. For a short time the experimental subject suffered a complete cardiac arrest, but after 90 seconds open-heart massage was used and heart started to work again. Halushka sued the university and the doctors and won the case. The judge held that experimentation was justified only if there had been informed consent. The consent given was invalid because of the incomplete information concerning the new drug used and the catheter advanced to the heart. An experimental subject was entitled to at least the same information as that given to a patient.

C. Declaration of Helsinki (1962/1964)

In the first half of the sixties the World Medical Association issued the Declaration of Helsinki concerning the biomedical research on human beings. The declaration was supposed to take the place of the Nuremberg code which had obvious shortcomings. At the same time the World Medical Association changed the emphasis from the freely given consent to the more paternalistic approach, that the advantages should outweigh the risks. Informed consent then appears as the second requirement for medical research. In some cases of clinical research combined with professional care even personal consent was not required which allows therapeutic experimentation even on unconscious patients.[17] It distinguished between purely scientific research and therapeutical experimentation. In both cases a proper relation between advantage and risk on the one hand and informed consent on the other is required. This becomes evident in two pertinent cases, one German[18] and one American.[19]

A German soldier had been treated at the Heidelberg University Hospital during the war because of an injury that had caused an aneurysm of the femoralis. A few times an arteriography had been performed using Thorotrast. Despite an occasional warning in the late thirties that Thorotrast might have long-range severe side effects the Greek chief of service decided to try it out on many soldiers to dispel the cloud hanging over Thorotrast. The soldier suffered a cirrhosis of the liver. He sued Heidelberg University and won his case. The court concluded that the arteriographies had been mostly research, since the health of the soldier was in no way helped by doing more than one arteriography. Since the soldier had not been informed and not given his consent to the

16 (1965) 52 WWR 608 (CA Saskatchewan).

17 The text of the 1964 Declaration of Helsinki concerning clinical research is reprinted in the *Report of the Cervical Cancer Inquiry* above n1, 132.

18 German Federal Supreme Court, 2 Feb. 1956. BGHZ 20,61.

19 *Fiorintino* v *Wenger* 227 NE 2d 296 (NYCA 1967).

experimental procedure, but on the other hand had been under military orders and could not have refused, he was awarded a substantial sum not as damages, but as compensation for having sacrificed his personal rights by acting as an experimental subject while under command of the army.

A fourteen year old boy had an operation performed for the purpose of correcting a scoliotic condition. The orthopaedic surgeon employed a method which he himself had developed five years ago and that had not been recognised generally. Up to that date 35 operations had been performed according to this method. One patient had died and four serious mishaps had occurred. The operation on the boy did not succeed. The court gave judgment for the plaintiff. The surgeon had not informed the parents of the fact that a new and unorthodox method was being used and that there had been a particular risk.

D. Revised Declaration of Helsinki (1975/1983)[20]

In 1975 the Helsinki Declaration on Biomedical Experimentation was totally revised by the World Medical Association in Tokyo. There was a group of Scandinavian doctors headed by Povl Riis from Copenhagen who submitted a draft to the assembly in Tokyo. The so-called Revised Declaration of Helsinki of 1975 is the most modern international instrument to deal with medical research. It is universally accepted because it makes the necessary distinction between therapeutical research and purely scientific experimentation; it insists on a medically acceptable benefit-risk ratio; it requires the informed consent of the subject; it installs ethical committees, and finally it requires publishers of learned journals to assess the ethical propriety of medical research papers submitted. One of the hotly debated issues at Tokyo concerned the set-up and function of ethics committees. The draft had proposed that the committee should have the power to review, allow or deny the application. The European delegations on the other hand were successful in changing the role of the ethical committee from review to advice. The section concerning ethic committees now reads:[21]

> The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

The institution of ethical committees came mostly into being by two occurrences in the United States. One was the famous article by Beecher in 1966 concerning ethics in clinical research.[22] This paper proved that at least 12 research protocols out of 100 clinical trials, documented in the very same journal, had been ethically questionable.

20 Judge Cartwright in the *Cervical Cancer Inquiry Report* prints both versions of the Helsinki Declaration at pp132 and 265. From the text of the report it seems that she was not aware of the totally new draft of the Helsinki Declaration in 1975. In 1983 just one subparagraph was added.

21 Revised Declaration of Helsinki I 2.

22 Beecher "Ethics and Clinical Research" (1966) 274 New England Journal of Medicine 1354.

The other factor that helped to bring the human subject protection committees or institutional review board into life was two cases.

The first of the cases was *Hyman* v *Jewish Chronic Disease Hospital.*[23] In 1963 the Sloane-Kettering Institute for Medical Research in New York approached the Jewish Chronic Disease Hospital in Brooklyn. The aim was a medical trial to establish whether chronically ill patients had the same ability to reject foreign tissue as healthy persons. The test was unrelated to their normal therapeutic programme. Twenty-two chronic patients had live cancer cells injected. They had just been asked whether they agreed to participate in a test that was to test their immune reaction. They did not know that it was a purely scientific experiment and that live cancer cells were to be used. The court found that a director of the hospital corporation was entitled as a matter of law to inspect the records of the hospital to investigate the facts of alleged illegal and improper experimentation on patients.

The second important case was noted in "Syphilis in the deep south", *Newsweek* 20 July 1981. Since 1929 Salvarsan had been used in southern states of the United States to treat syphilis. From 1932 there was a programme by public health agencies that for four decades studied the results of untreated syphilis in contrast to medication. The patients in the study group did not receive Salvarsan or later Penicillin. The survivors instituted civil proceedings and were paid 10 million dollars by the government in 1974.

The function of the ethical committee is to safeguard the rights of the patient and/or experimental subject. In the second instance the committee should control the researcher who sometimes transgresses the rights of the patient in his desire to establish a new treatment or to achieve a goal in scientific research. Finally even the institution where the research is to be performed should be protected by the deliberations of the ethics committee. Up to now it is still questioned how far an ethics committee is entitled to look into the scientific validity of the research protocol. Sometimes it is simply assumed that the committee has to review everything including the scientific design of the study.[24] Many ethical committees concern themselves mostly with ethical and legal questions. But it is generally agreed that experimentation without scientific merit is also unethical. On the other hand an ethics committee should not act as a scientific committee and interfere if the research protocol is just questionable or if there could be other ways and means of achieving the results.

III. MEDICAL EXPERIMENTATION : MORE OR LESS

The medical treatment of today is based on the experimentation of yesterday. To assure the steady progress of medicine, it is necessary to undertake medical research on a broad range. Medical experimentation should be assisted and not unduly burdened. The latter would be the case if unnecessarily stringent rules were to apply to medical experimentation. In biomedical research the role of the lawyer is mostly concerned with consent and procedure. Therefore I will look into the conclusions and recommendations

23 206 NE 2d 338 (CA, NY 1965).
24 As in the *Report of the Cervical Cancer Inquiry* above n1, 145.

of the Report of the Cervical Cancer Inquiry in New Zealand. The highly impressive report by Judge Silvia Cartwright invites discussion and dissent in three respects.[25]

(a) *Findings and recommendations-5.b (ii)*

> General information on therapeutic or non-therapeutic research should be offered to all patients whose permission is sought for inclusion in a trial. Their written consent must be sought on all occasions when interventionist clinical or non-therapeutic research is planned.

The absolute language of the second sentence seems to preclude medical research on unconscious persons and the mentally ill. Especially with regard to research in the field of cardiovascular illnesses that language should be toned down to allow clinical experimentation with assumed consent on unconscious persons. The Revised Declaration of Helsinki allows this type of clinical research in II.5.:

> If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

(b) *"Written consent"*. There is no legal precedent that the consent of the patient or experimental subject should be given in writing. On the other hand a statute can specify that consent has to be given in writing. In the absence of a statute written consent can help to establish evidence that the patient has agreed. In the daily practice of medical experimentation it has been shown, however, that a checklist given to the doctor and used by him in informing the patient verbally is at least as useful as a written consent form. In a conversation with the patient the physician can establish whether the patient really understands what the experimentation and its procedures are about. If the patient then still agrees, he may do so in writing, orally or just by taking part in the experimentation. All this means that consent just follows information in importance. If the experimental subject after having been informed participates freely in the trial there is no case in tort, even if the consent has not been given in writing.

(c) *"Lay representation on the ethical committee [should approximate] one half of the membership"*[26]. Ethics committees started out with the peer review system, where other doctors and researchers reviewed research protocols. Now the community review model is preferred in which researchers and physicians are joined by one, two or at the most three members not involved in research or treatment. To require that one half of the ethical committee is composed of laymen is an unnecessary extreme.[27] Judge Cartwright talks of the modern trend towards increased lay participation in ethical assessment and refers to a recommendation in Australia according to which a woman, a man, a minister of religion, a lawyer and a medical graduate without research experience shall function as lay members of an ethics committee established by the medical

25 Above n1, 146 et seq.
26 Recommendation 5.c(v)(d) of the Cartwright Report
27 See now "Standard for Hospital and Area Health Board Ethics Committees Established to Review Research and Treatment Protocols" (Department of Health, Wellington, October 1988) para 3.2 [Ed].

research council. But what would be the task of these venire-persons? Research protocols are often lengthy and very technical. They go sometimes deeply into statistics and can be framed in a foreign language. Usually it takes a researcher to understand a research protocol. Lay members after a while will have adjusted to the work and some of them will be able to understand the less complex research procedures. But to up-grade the lay members from their watch-dog function to the role of overseer of scientific experimentation is not advisable. Lay members are there to guard against the danger of a closed shop of the scientists. It is of no use to give the lay members the voting power to inhibit experimentation. Especially if the ethics committee has first to enquire whether the study is scientifically valid as the Report states, the lay members are not called for. Let us not limit medical experimentation too much. The medical research of today is the medical treatment of tomorrow.