Informed consent in human experimentation before the Nuremberg code

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This Nuremberg issue of the BMJ comprises seven papers in this special section, editorials by Jennifer Leaning and Donald Acheson, two personal views, four news items and three book reviews. In addition, we are publishing on pp 1448-9 the Nuremberg code from 1947 and the Declaration of Helsinki that was derived from it. All the Nuremberg material is available on the BMJ's homepage: http://www.bmj.com

The issue of ethics with respect to medical experimentation in Germany during the 1930s and 1940s was crucial at the Nuremberg trials and related trials of doctors and public health officials. Those involved in horrible crimes attempted to excuse themselves by arguing that there were no explicit rules governing medical research on human beings in Germany during the period and that research practices in Germany were not different from those in allied countries. In this context the Nuremberg code of 1947 is generally regarded as the first document to set out ethical regulations in human experimentation based on informed consent. New research, however, indicates that ethical issues of informed consent in guidelines for human experimentation were recognised as early as the nineteenth century. These guidelines shed light on the still contentious issue of when the concepts of autonomy, informed consent, and therapeutic and non-therapeutic research first emerged. This issue assumes renewed importance in the context of current attempts to assess liability and responsibility for the abuse of people in various experiments conducted since the second world war in the United States, Canada, Russia, and other nations.

POPPERFOTO

Albert Neisser, 1855-1916

First Prussian directive on informed consent

The introduction of scientific and experimental methodology into clinical medicine in the nineteenth century brought with it an increased demand for experimentation on human subjects, particularly in bacteriology, immunology, and physiology. This research was done mainly on patients in hospital, often without their consent, under an "ethos of science and medical progress." As a result of injury to some patients subjected to non-therapeutic research, however, controversy and public debate ensued about the ethics of human experimentation.[1-4]

In 1891 the Prussian minister of the interior issued a directive to all prisons that tuberculin for the treatment of tuberculosis "must in no case be used against the patient's will."[5] But the first detailed regulations about non-therapeutic research in Western medicine came from the Prussian minister for religious, educational, and medical affairs in 1900. They were issued after critical public discussion and political debate on the Neisser case in the Prussian parliament and set forth the legal basis of disclosure and unmistakable consent.[1,2] Of particular interest is the debate within the medical profession and the political circumstances.

The Neisser case

In 1898 Albert Neisser, discoverer of the gonococcus and professor of dermatology and venereology at the University of Breslau, published clinical trials on serum therapy in patients with syphilis. In order to find a method of syphilis prevention he injected cell free serum from patients with syphilis into patients who were admitted for other medical conditions. Most of these patients were prostitutes, who were neither informed about the experiment nor asked for their consent. When some of them contracted syphilis Neisser concluded that the "vaccination" did not work. However, he argued that the women did not contract syphilis as a result of his serum injections but contracted the disease because they worked as prostitutes. Liberal newspapers published these and other cases, triggering public debate.

Most academic physicians at the time supported Neisser. An exception was Albert Moll,[6] a psychiatrist in private practice in Berlin, who collected in his *Physicians' Ethics* 600 cases of unethical non-therapeutic research on humans and emphasised the need for informed consent. Moll also developed a legally based, positivistic contract theory of the patient-doctor relationship, which is widely ignored in current bioethics publications.[7]

In 1898 the public prosecutor investigated the case, and Neisser was fined by the Royal Disciplinary Court. The court ruled that, though Neisser as a well known medical authority may have been convinced that the trials were harmless, he should have sought the patients' consent. Not questionable science but lack of patients' consent was the main principle for the legal judgment.

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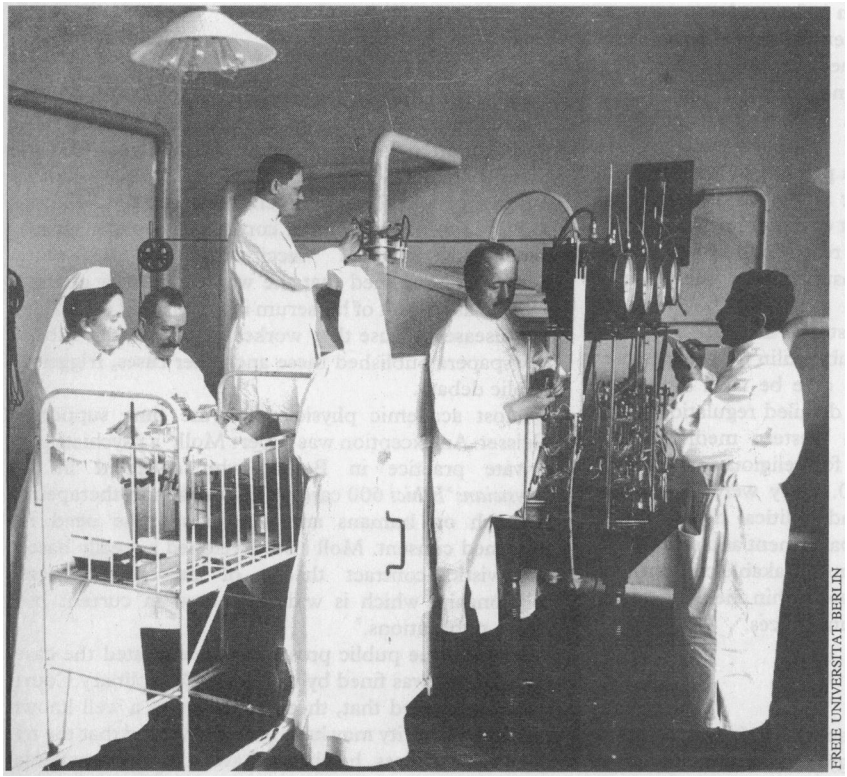
GOVERNMENT ACTION

The Prussian parliament also discussed the case several times and in 1899 asked the government to act. As a result the minister for religious, educational, and medical affairs commissioned a detailed report from the Scientific Medical Office of Health, which was composed of leading German physicians such as Rudolf Virchow. The commission directed its attention to beneficence and autonomy. It concluded that a physician who recognised that an injected serum might cause infection had no right to inject such a serum. In any case, both informing the subject and obtaining the subject's consent were preconditions to experimentation. In a handwritten report Emil von Behring argued that, particularly with reference to the Neisser case, self experimentation should always precede experiments on patients. He personally held that purely scientific experimentation on human subjects was unethical even if they gave voluntary consent.[1 4]

The minister also sought legal advice on the Neisser case. Lawyers stated that conducting non-therapeutic research on a subject without consent fulfilled the criteria for causing physical injury in criminal law. The scientific validity of the experiment did not serve as mitigation. Informed consent was a mandatory precondition for any non-therapeutic research. Problems of coercion, persuasion, and the unequal authority between doctor and patient were discussed in detail, and the lawyers concluded that respect for rights and morality had the same importance for the good of mankind as medical and scientific progress. Written documentation and clear responsibility of the medical director for all human experimentation became legal doctrine.

Finally, in 1900 the minister for religious, educational, and medical affairs issued a directive to all hospitals and clinics. Medical directors were advised that all medical interventions other than for diagnosis, healing, and immunisation were excluded under all circumstances if "the human subject was a minor or not competent for other reasons" or if the subject had not given his or her "unambiguous consent" after a "proper explanation of the possible negative consequences" of the intervention. All research interventions could be performed only by the medical director or with his or her authorisation. In all cases fulfilment of these requirements as well as all further circumstances of the case had to be "documented in the medical history."[1] Despite all this, however, the directive was not legally binding and little is known of its impact on human experimentation.



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Medical experimentation on a metabolic ward of the Kaiserin Auguste Victoria Haus, Berlin, in the 1920s

Circular of the Reich minister of the interior: guidelines for new therapy and human experimentation, 1931

Because of criticism of unethical human experimentation in the political press and in parliament as well as in the context of a political reform of criminal law in Germany, in 1931 the Reich government issued detailed "guidelines for new therapy and human experimentation." The guidelines clearly distinguished between therapeutic ("new therapy") and non-therapeutic research ("human experimentation") and set out strict precautions.

Besides the principles of beneficence and non-maleficence, the regulations were based on patient autonomy and a legal doctrine of informed consent. "New therapy may be applied only if consent or proxy consent has been given in a clear and undebatable manner following appropriate information. New therapy may be introduced without consent only if it is urgently required and cannot be postponed because of the need to save life or prevent severe damage to health. . . ." In those cases a written report must clearly outline the preconditions. But non-therapeutic research was "under no circumstances permissible without consent."[8 18] Written documentation and a clear structure of responsibility for each clinical trial were required. Though an early model of institutional review boards was discussed, the official guideline adopted the hierarchical model from the directive of 1900, in which the medical director was responsible for all clinical research in the institution.

As later formulated in the Nuremberg code, a careful cost-benefit calculation and a detailed research plan with animal experimentation beforehand were already required to minimise risk to human subjects. Some regulations were even stricter and more detailed than those contained in the Nuremberg code and the much later Declaration of Helsinki. Human experimentation on dying patients was absolutely prohibited. Publication of the results of new therapy must respect the patient's dignity and the mandate of humanity. In academic teaching every opportunity should be taken to emphasise the special responsibilities of a physician undertaking clinical trials. Even further, any exploitation of social or economic need in testing new therapies was rejected.

Discussion

This paper shows that explicit directives concerned with the welfare of people subjected to medical experimentation in Germany were in place long before the Nuremberg code was devised in 1947.[9-12] Critical press reports and debate in parliament forced the Prussian government to issue the first directive concerned with medical experimentation in humans in 1900. This directive was based on medical and legal scientific reports. A clear distinction was made between therapeutic and non-therapeutic research, but regulations were issued only for non-therapeutic research. The regulations were based on the principle of autonomy and represented an early model of informed consent. A "proper explanation of the possible negative consequences" of the intervention and "unambiguous consent" became the mandatory standard. In addition,

legal reports carefully discussed aspects of coercion, persuasion, and imbalance of authority between patient and doctor just as in contemporary work.[13] Minors and incompetent subjects were generally excluded from non-therapeutic research, as they could not give valid informed consent.

We conclude that at the turn of the century informed consent was already a legal doctrine in medical experimentation in Germany, being based on "unambiguous consent" of the subject after "proper" information had been given by the doctor, including negative consequences and side effects. Interestingly, the regulations were not initiated by doctors or research institutions but were issued by government authorities. However, it remains an open question how informed consent was applied by doctors in research and clinical practice and how it shaped the individual doctor-patient relationship.[14-16]

The guidelines issued by the Reich government in 1931 regulated therapeutic and non-therapeutic research in human subjects. Whereas without exception non-therapeutic research could be performed only with the subject's informed consent, therapeutic research could be performed without explicit consent but only in a medical emergency and if it was deemed to be in the patient's best interest.

The second part of the Prussian directive of 1900 defined a structure of responsibility in medical institutions. Because of the hierarchical structure in German hospitals only the medical director and physicians authorised by the medical director were allowed to conduct research on human subjects. However, in no case of injury to a patient by experimentation was the issue of responsibility controversial, as all medical directors and professors declared their personal responsibility. This hierarchical model of responsibility, also found in the Reich government's guidelines of 1931, differs from the modern concept of responsibility in clinical research. Under current concepts the individual researcher is personally responsible for his or her actions and ethical issues are assessed by peers on institutional review boards.

For the first time in history informed consent, the research process, and explicit clarification of personal responsibility for the experiment were required to be included in the medical record. In addition, issues of written research plans with a risk-benefit assessment, the need for previous animal experimentation, and medical self experimentation were raised. Though a system of public health insurance existed in Germany in 1931 and provided good health care for all citizens, issues of social justice and the protection of poor people in medical research were regulated. We question whether the healthcare system in the United States would meet these regulations, many patients without health insurance having no access to regular medical treatment. In order to obtain medical help these patient must rely on free experimental treatment in research institutions without having a choice whether to give free and autonomous informed consent.

Though present conceptions of informed consent differ from those in the Prussian directive of 1900 and the Reich government's guidelines of 1931, some basic elements can be identified in postwar regulations[17 18] together with many ethical issues of human experimentation.[19-23] Our primary objective was to show that the basic concept of informed consent was developed long before the second world war and before Nazi crimes in Germany, not on the initiative of the medical profession or research community but as a legal doctrine by government authorities. The guidelines of 1931 were not annulled in Nazi Germany, when unethical experiments were performed by German doctors in concentration camps. Though no other nation seems to have had such ethically and legally advanced regulations at the time, these did not prevent crimes against humanity by part of the German medical profession.[9-12]

Key messages

- The Nuremberg code of 1947 is widely regarded as the first document providing ethical regulations in human research on the basis of informed consent
- New research has uncovered ethical issues of informed consent in human experimentation as early as the nineteenth century
- Regulations were not initiated by the medical profession but were issued after critical public discussion and political debate
- Basic elements of the modern legal concept of informed consent can be found in these early regulations
- These early regulations were not binding in the legal sense and little is known about their actual impact on clinical research

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The Nuremberg Code (1947)

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects.

PERMISSIBLE MEDICAL EXPERIMENTS

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Taken from Mitscherlich A, Mielke F. *Doctors of infamy: the story of the Nazi medical crimes*. New York: Schuman, 1949: xxiii-xxv.

Declaration of Helsinki (1964)

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the law of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. 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.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

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 (1, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.