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Ethics of studies involving human volunteers. I. Historical background

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Synopsis

The evaluation of personal products using panels of human volunteers is crucial to the continued development of the industry. Nowadays, however, it is increasingly important to ensure that such studies are both safe for the participants and are ethical. As a means of defining general rules for judging and justifying the ethics of human testing, historical milestones in the development of human experimentation are given. While most experience originates from biomedical research, findings help establish standards of ethical review of non-therapeutic human testing used in the cosmetics industry.

INTRODUCTION

In order to meet ever-demanding consumer expectations and to survive in a competitive business environment, the cosmetics and toiletries industry constantly strives to create novel or improved formulations to delight their customers. No matter how superior innovative personal products can be shown by laboratory investigations, such scientific support will, however, fail to translate into sales unless consumers perceive the benefits firsthand during use, and without experiencing gross negatives. This, together with legislation and moral obligations to prevent product testing on animals, results in the development program progressing rapidly from bench experiments to efficacy and sensory trials in healthy human volunteers. With the increasing technical complexity of personal care products and the claims made for them, the boundaries of testing carried out on volunteers are constantly expanded. The industry has a good reputation in conducting such studies *safely,* but it is also important for the experimenter to consider the *ethical* aspects of research on human volunteers and to demonstrate high ethical standards for these investigations.

The present paper provides a brief review of the history of ethics associated with experiments on humans to further aid appreciation of the requirements for the personal products industry to be discussed in Part II (this issue).

HISTORY OF RESEARCH ETHICS

Ethics are the moral principles governing the conduct of a particular activity. As morals are accepted behavioral patterns dictated by the society, they change as societies vary temporally and geographically. Most of the very early experimentation on man was done with medical disciplines in mind (anatomy, physiology, pathology, etc), and it is only in more recent times that research has become focused on consumer benefits. While these are key to the progress of the consumer goods industry, special consideration should be given to the risk benefit analyses of such work.

The impetus for human testing originates from the advancement of medical knowledge, with examples dating back to Hippocrates, who observed movements in the contralateral side of a child's body as he scratched the surface of the cortex from which he was removing bone splinters (1). Early reports of concern for the ethics of such work date back *ca* 2000–2500 years. A Persian prince in the second century AD advised a medical student to "experiment freely, but not on people of high rank or political importance" (2).

The Hippocratic oath, written between 470 and 360 BC, states

> I will follow that system of regime which, according to my ability and judgment, I consider for the benefit of my patients and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to anyone if asked, nor suggest any such counsel.

Its scope does not include "experimentation," which was only first addressed in the 18th century in *Medical Ethics* by the English physician Percival (3a). He acknowledged the *need* for medical research with judgment of the ethical validity of experimental procedure based on test design, its basis in established or analogous theory, and on peer review and expert advice:

> Whenever cases occur, attended with circumstances not heretofore observed, or in which ordinary modes of practice have been attempted without success, it is for the public good, and in especial degree advantageous to the poor (who, being the most numerous class of our society, are the greatest beneficiaries of the healing art) that new remedies and new methods of chirugical treatment should be devised but, in the accomplishment of the salutary purpose, the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well-authenticated facts. And no such trials should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case.

Given the paternalistic culture prevailing within the medical profession at the time, it is not surprising that even these principles ignore important ethical considerations such as protection of the subjects and their consent to procedures to which they may be subjected. Reference to the benefits for the poorest members of society is surprising since at the time medical care would have been beyond their grasp, unless this amounts to tacit direction to use the poor for experimentation.

Beaumont in 1833 performed numerous non-therapeutic human studies into gastric physiology. Like Percival, he required that the investigator be conscientious and responsible and that the experiment be well planned, methodical and designed to provide the maximum amount of information possible. He extended Percival's code by incorporation of the need for voluntary (if not informed) consent and showed concern for the subject's well-being (4): "The experiment is to be discontinued when it causes distress to the subject." He also addressed risk-benefit analysis.

However, based on the Christian doctrine of "do no ill to thy neighbor," Claud Bernard, a French physiologist and ethicist, in 1927 developed a code (5) forbidding experimentation on man which "might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e. to the health of others." He concluded, "among the experiments that might be tried on man, those that it can only do harm are forbidden. Those that are innocent are permissible and those that may do good are obligatory." This effectively ruled out all non-therapeutic human studies.

To establish the possibility of immunizing against syphilis by inoculation with serum from syphilitic patients, Albert Neisser in 1892 used, without their full knowledge and consent, three adolescent prostitutes as the test group and four healthy children as the control group. The prostitutes developed syphilis. This otherwise renowned scientist was fined and ordered to pay significant costs and his reputation was tarnished. The well-publicized study led in 1900 to the first governmental position on research using human subjects (6). It states

> (I) . . . medical interventions for purposes other than diagnosis, therapy and immunization are absolutely prohibited, even if all other legal and ethical requirements . . . are fulfilled if:
> The person in question is a minor or is not fully competent on other grounds
> The person concerned has not declared unequivocally that he consents to the intervention
> The declaration has not been made on the basis of a proper explanation of the adverse consequences that may result form the intervention
>
> (II) In addition . . .
> Interventions of this nature may only be performed by the director of the institution himself or with his special authorization
> In every intervention of this nature an entry must be made in the medical case-record book, certifying that the requirements laid down in Items 1–3 of section 1 have been fulfilled, specifying details of the case.
>
> (III) This directive shall not apply to medical interventions intended for the purpose of diagnosis, therapy and immunization.

This Prussian directive provides for informed consent, delineates non-therapeutic and therapeutic research, and offers protection for the most vulnerable groups against use in non-therapeutic experiments. It reinforces the ethos of the competency of the investigator and of peer review by restricting the work to the unit director or his nominee. One of the weakest elements is the absence of risk-benefit considerations since there is no requirement for the investigator to weigh the risks to the subject in relation to any benefits to society. The nearest assessment is that conducted by the volunteers themselves, who decided whether or not to consent after being informed of the hazards.

The rapid expansion of the pharmaceutical industry in Germany during the 20th century brought about a shift from ad hoc, small-scale, individual physician-controlled investigations to widespread industry-controlled research. Despite the existence of the comprehensive German directive, research trials were frequently criticized in the German press, and following the death of 75 children in a program of studies on tuberculosis vaccines, the Reich Minister of the Interior published guidelines (3b,7) in 1931, key elements of which include

- All staff entering into employment must sign the guideline
- An explanation provides for the need for therapeutic and non-therapeutic research
- Confirmation that responsibility for the "life and health" of the subject rests with the physician

- A requirement for risk-benefit considerations with adequate animal experimentation to underpin the human studies
- A need for informed consent from the subject or legal guardian
- Provision of special consideration for vulnerable groups such as children and those with social hardship
- Creation of special cases when using live micro-organisms
- The responsibility of the unit director should be highlighted
- A requirement for the work to be written up in a report and documentation of the consideration given to ethical justification of the study
- The need for work to be published while maintaining the dignity of the subject (the first allusion to the confidentiality of the subject)
- Additional constraints for non-therapeutic research:
    (a) Prohibition where consent was not obtained
    (b) Primacy and preference for laboratory and animal studies to generate data to either negate the need for human experiments or to ensure the validity of the human study
    (c) Prohibition of studies on minors if there is any risk to the child
    (d) Prohibition of tests on the dying
- Provision of an ethical imperative to carry out research where current known methods are likely to fail
- Academic training for physicians carrying out research, in the ethical and scientific aspects of their studies and in their publication

Fewer cases of unethical experiments on humans have aroused so much widespread public condemnation than the Nazi atrocities during the Second World War (3b). Twenty-three physicians stood trial for war crimes and crimes against humanity. Experiments had ranged from determining for military purposes the survival period at sub-zero temperatures or low atmospheric pressure, to the assessment of the efficacy of antibiotics and immunization therapies. Malaria experiments resulted in 30 deaths from malaria and a further 300–400 from complications. Female prisoners were given simulated battle wounds and deliberately infected with gangrene to determine the efficacy of sulphanilamide; many died and others were left permanently disabled. Vast collections of human skeletons and organs were amassed to perform anthropological measurements and to study racial specificity. Programs included forced sterilization of Jews, Gypsies, and Poles of child-bearing age using drugs and concealed X-ray units.

Less macabre experiments had been conducted elsewhere, including 15,000 criminals and mentally-ill subjects forcibly rendered sterile in the USA (3b). Indeed, the French Nobel Laureate Alexis Carrel suggested (3b) that criminals and the mentally ill should be "humanely and economically disposed of in small euthanasia institutions supplied with the proper gases." Studies to determine the effect of withdrawing various quantities of blood from subjects were conducted in the US (8) and Germany. In the UK, experiments into the spread and treatment of scabies were performed on volunteers drawn from conscientious objectors to the war (9). Despite the availability of guidance material, unethical studies were still being conducted, e.g.,

> Children with learning disabilities at Willowbrook School were deliberately infected with hepatitis in order to follow its natural history. It was claimed that the parents of the children consented. However, the information provided to them was deliberately deceptive as it made the inoculations appear to be part of a vaccination programme (10).

> In the Tuskegee syphilis experiment 400 poor, black syphilis-positive subjects were studied without treatment even though cheap effective therapy became available. They were not informed about the study but told that they had "bad blood." Their participation was secured by promises of free transport and lunch on "study days" and free medical care and burial after autopsy. This led to guidelines for Institutional Review Boards on the peer review of protocols and the ethical principles which should underpin their decisions (11).
>
> Cancer cells were injected into elderly debilitated patients in a New York hospital. The work was funded by the US National Institutes of Health and the case was the subject of an enquiry (10).
>
> Parents of premature babies reported that their infants had been included in a research study of a ventilator without their knowledge or consent (12).
>
> At one hospital over 2000 organs were removed from 800 children purportedly for research purposes without their parents' knowledge (13).

As a result of such events, including the Thalidomide tragedy, a raft of codes appeared, including the Nuremburg Code (1947), the World Medical Organization's Declaration of Helsinki (1964 and subsequent amendments), the US National Research Act (1974), and the Belmont Report (1979).

The Nuremburg Code championed informed consent. It has been argued that this code is based on experiments conducted during wartime and that the experiments were neither ethical nor intended so to be (c.f. with Operation Desert Storm when US military were exempted from the need to gain informed consent when administering a range of therapies to soldiers).

The US National Research Act stipulates that all federally funded research must first receive ethical review by Institutional Review Boards (IRBs). The scope and responsibilities of IRBs are given in Title 21 of the Code of Federal Regulations, Parts 50 and 56, and in Title 45 of the Code of Federal Regulations, Part 46. There is a requirement to follow the Declaration of Helsinki or the Belmont report.

The Belmont report (14)

- differentiated between research and accepted therapy
- addressed basic ethical principles (respect for persons, beneficence, and justice)
- reviewed application of general ethical principles (informed consent, risk/benefit assessment, and subject selection)

The Declaration of Helsinki is also a set of principles, which include the following dicta:

- Biomedical research on humans must conform to accepted scientific principles and be based on data from animal experiments and the literature.
- The proposals should be in clearly written clinical protocols for review by ethics committees independent of the sponsor and investigator. The protocol should contain a statement of the ethical considerations involved and confirm compliance with the Declaration.
- Trials should be conducted and supervised only by suitably scientifically/medically qualified staff: responsibility for the subjects rests with a medically qualified person and not the subjects themselves.
- The importance of the objective must be in proportion to the inherent risk to the subject. Assessment of predictable risk should be considered against foreseeable benefits to subjects or to others. The interest of the subject must prevail over the interest of science or society.

- The subjects' privacy must be assured. The impact of the study on the subjects' physical and mental integrity and on their personality must be minimized.
- Hazards must be predictable.
- The accuracy of the results of such research must be preserved in publications.
- Subjects must be informed about the study and of their right to abstain or withdraw: they must give consent (preferably in writing).
- Informed consent must be obtained by a physician independent of the subject.
- Informed consent should be obtained from a legal guardian in the case of legal incompetence. Informed consent from the responsible relative is necessary for minors, where physical or mental incapacity make it otherwise impossible for the subject to give informed consent. Minors should also give their own consent where this is possible.

Additional principles are listed for medical research combined with professional care, and the following principles are emphasized for non-therapeutic (non-clinical) biomedical research on human subjects:

- The physician remains the subject's protector.
- Subjects should be volunteers who are healthy persons or patients for whom the research is not related to their illness.
- The investigator team should cease the work if the study would harm the subject.
- The interest of science and society should never take precedence over a subject's well-being.

The concept of scientific peer review of research proposals was strengthened by the 1975 amendment to the Helsinki declaration.

In the UK a system of local research ethics committees and multi-center research ethics committees have existed for NHS research since 1966 and 1997, respectively. A requirement for peer review appeared in the 1967 Royal College of Physicians guidelines (15). They later issued *Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects* (16). These are somewhat biased towards the researcher, with an instruction to ethics committees to be ever aware of the need to avoid impeding good medical research. The College also published a report, *Research on Healthy Human Volunteers* (17).

Recently, the UK implemented the EC "clinical trials" Directive 2001/20/EC with promulgation of *The Medicines for Human Use (Clinical Trials) Regulations 2004.* Under these regulations no person shall be permitted to conduct a clinical trial unless there has first been a favorable opinion obtained from an ethics committee. The UK Ethics Committees Authority is responsible for establishing, recognizing and monitoring UK ethics committees, though this relates to those committees reviewing trials on medicinal products only.

Good clinical research practices have been produced throughout the developed world, and a major milestone was publication of the guidelines from the International Conference on Harmonization of GCP, which attempt to standardize requirements for Europe, Japan, and the USA. These address ethical considerations for licensed trials (18).

CONCLUSION

Philosophical theories abound ranging from consequentialism (the morals of an action should be judged on the basis of the consequences that follow) to deontological theories (which judge the morality of an action on the original intentions, motivations, and obligations it seeks to fulfill, i.e., the end does *not* justify the means). During the past 2000 years fundamental principles have emerged on the ethical standards for medical research on human subjects. The implications of these general ethical rules for non-medical bio-research are discussed in Part II.

REFERENCES

(1) J. Katz (Ed.), *Experimentation with Human Beings* (Russel Sage Foundation, New York, 1972).

(2) R. Platt, The ethical basis of medical science, *Sci. Basis Med. Ann. Rev.,* 1–15 (1966).

(3a) C. D. Leake (Ed.), *Percival's Medical Ethics* (Williams and Williams, Baltimore, 1927).

(3b) G. J. Annas and M. A. Grodin (Eds.), *The Nazi Doctors and the Nuremberg Code* (Oxford University Press, 1992).

(4) H. Beecher, *Research and the Individual Subject* (Little Brown and Co, Boston, 1970).

(5) C. Bernard, *An Introduction to the Study of Experimental Medicine;* translated by H. C. Green (Macmillan, New York, 1927).

(6) J. Vollmann and R. Winau, The Prussian regulation of 1900: Early ethical standards for human experimentation in Germany, *IRB a Review of Human Subjects Research,* 18(4), 9 (1996).

(7) Anon, *Int. Digest Health Leg.,* 31, 408–411 (1980).

(8) J. Warren, *et al.,* The effect of venescetion and the pooling of blood in the extremeties on atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances, *Clin. Invest.,* 24(3), 337–344 (1945).

(9) K. Mellanby, *Human Guinea Pigs* (Blackfriars Press, Leicester, 1945).

(10) H. K. Beecher, Ethics and clinical research, *N. Eng. J. Med.,* 274, 1354–1360 (1966).

(11) *Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel* (US Government Printing Office, Washington, DC, 1973).

(12) NHS Executive West Midlands Regional Office, *Report of a Review of the Research Framework in North Staffordshire Hospital NHS Trust* (Griffiths Report) (Leeds, NHS Executive, 2000).

(13) *The Royal Liverpool Children's Inquiry, January 2001* (The Stationary Office, 2001).

(14) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Department of Health, Education and Welfare, Washington, DC, 1979).

(15) C. Bassiouni, T. G. Baffes, and J. T. Evrard, An appraisal of human experimentation in international law and practice: The need for international regulation of human experimentation. *J Crim. Law Criminol.,* 72(4), 1597–1666 (1981).

(16) Royal College of Physicians, *Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects* (Royal College of Physicians, London, 1990).

(17) Royal College of Physicians, *Research on Healthy Human Volunteers* (Royal College of Physicians, London, 1986).

(18) *ICH Guideline for Good Clinical Practice* (International Federation of Pharmaceutical Manufacturers Associations, Paris, 1996).