CEE ACP Cohort V Proseminar
Vilnius, August 18-23, 2014

ON DEVELOPMENT OF BIOMEDICAL RESEARCH ETHICS – SOME HISTORICAL INPUTS

Andres Soosaar
Verbitas LLC, Tartu, Estonia
CEE ACP Cohort I

What is research ethics?

Website of the Research Ethics Program, UC San Diego:

Research Ethics is defined here to be the ethics of the planning, conduct, and reporting of research.

It is clear that research ethics should include:

- Protections of human and animal subjects

What is research ethics?

Website of the Research Ethics Program, UC San Diego:

However, not all researchers use human or animal subjects, nor are the ethical dimensions of research confined solely to protections for research subjects. Other ethical challenges are rooted in many dimensions of research, including the:

- Collection, use, and interpretation of research data
- Methods for reporting and reviewing research plans or findings
- Relationships among researchers with one another
- Relationships between researchers and those that will be affected by their research
- Means for responding to misunderstandings, disputes, or misconduct
- Options for promoting ethical conduct in research

Nature of medicine

- In early times medicine was rather **art of healing**;
- Healers were people with **special abilities, creativity and intuition** to find psychological compromise between supranatural and natural forces of the world;
- Until the 20th centrury there weren't any unified approach to health care, instead medicine was rather a great patchwork of different local schools, ideas and practices.

Main dimensions of medicine

- **Health-disease distinction**

Basic principles are (i) existence of some norms and (ii) possibility to modify abnormal situations. Here are a lot of issues dealt by natural sciences and psychology.

- **The doctor-patient or therapeutic relationship**

An ideal situation would be that human relations are symmetrical but disease makes them clearly asymmetrical. Here are a lot of issues with varieties from psychology to different aspects of social life, including ethics.

Knowledge and compassion

- Medicine and its practicioners have had through all times very high demand for knowledge, skills and compassion.
- Commonsense says that knowledge is more needed in health-disease distinction area and moral sentiments are very important in therapeutic relationship.

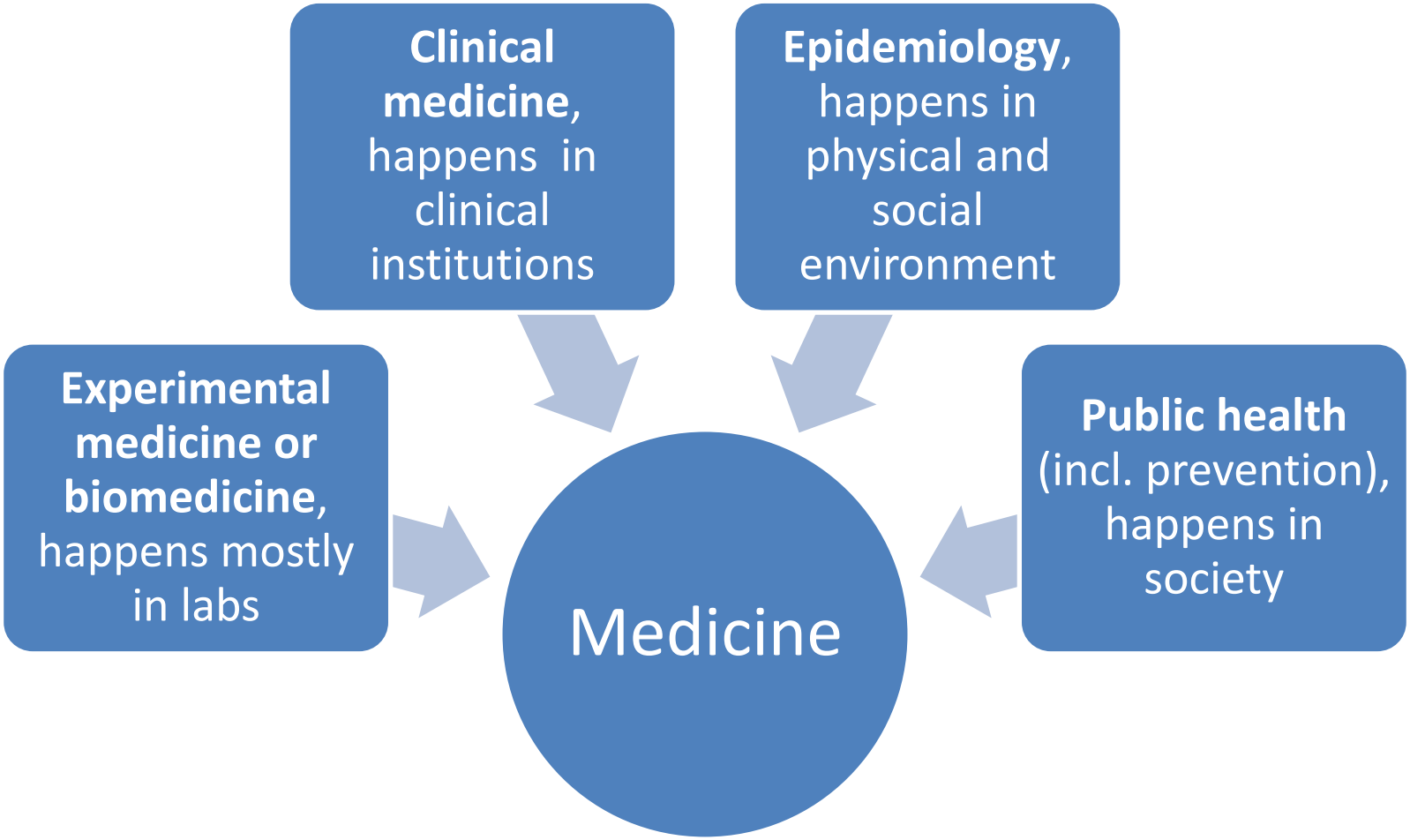
When did scientific medicine start?

- There are different types of medicine, but systematic medical research with clear demand on objectivity happens only in scientific medicine;
- Opinions about the beginning of scientific medicine are quite different, from Hippocrates era to 1990s when the ideology of evidence based medicine appeared and became fastly the dominating one.
- AS: Scientific medicine in a systematic way and with consolidating influence started in the 19th century.

Growing clinical experience and planned research

- Before 19th century clinical experience grew up mostly through **observations** on the place of therapy;
- Afterwards science of medicine turned rather **experimental** which is from scientific and moral point of view in interventions into integrity of persons much more demanding than observational approach.

Main areas of medicine



Development of medical research ethics

Sporadic history of researh ethics before 19th century I

- Principles of clinical ethics were also valid in medical research;
- Hippocratic Oath: … I will prescribe regimens **for the good of my patients** according to my ability and my judgment and **never do harm to anyone** …

Sporadic history of researh ethics before 19th century II

- The Golden Rule: *One should treat others as one would like others to treat oneself*
- John Gregory's modification (1772) of Golden Rule for human research: "dangerous experiments…I would ask that man if he have done so to his Child, if he would not do it to his own Child, why should he in danger the lives of other people".

Combination of therapy and research – an evergreen ethical dilemma in medicine

WMA Declaration of Helsinki (2013) #14: Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Is research on human beings avoidable in medicine?

- HD 2013 #5 on research imperative: Medical progress is based on research that ultimately must include studies involving human subjects.
- Animal research, use of different modelling techniques have been candidates to substitute human research, but have produced additional ethical problems in biomedical research.

Human research versus animal research

- Animals have been used long time as substitutes of human beings in medical research;
- Cartesian view that animals do not have mind (and feelings) justified long time vivisectionism and other forms of cruel behavior to animals;
- In 1959 Russell and Burch offered 3R's (**R**eplace, **R**educe, **R**efine) for animal experiments;
- Today experimentation on animals is carefully regulated.

Reserch ethics in the 19th century

- Russian doctor Vikenty Veressayev published in 1901 „The Memoirs of a Physician“ which chapters 7, 8 and 9 describe many unethical human experiments (including inoculation of STI and cancer) and use of vivisection on animals.
- At the same time he strongly defended the **research imperative**: „And I registered a vow in future only to employ those remedies upon my patients, which had stood ample test and left no room for doubt as to their effects.“

Other bad cases from 19th century medical research

- Albert **Neisser** (1855– 1916) identified *Neisseria gonorrhoeae* in 1879;
- He published in 1898 results of syphilis prevention study where serum of syphilis patients was injected without consent to 7 persons (mostly prostitutes) with other medical condition;
- He was convicted of crime of inflicting unlawful physical injury and fined of 1545 marks which was almost half of his annual salary.
- Gerhard **Hansen** (1841 – 1912) identified in 1873 *Mycobacterium leprae* as the causative agent of leprosy;
- He did an experiment without any consent, in which he introduced material from a leprosy nodule into the cornea of another person to prove its infectious nature;
- He was removed from practising for life by the court.

Human rights, justice and selection of research subjects

- As societies in the past have been quite unjust; exploitation, uncertainty and risks of research turned the role of a research subject rather a miserable and unwanted one and through all times participation in research has been connected to discrimination;
- In modern times we have seen the fight to involve some groups into research (**DoH 2013#13:** *Groups that are underrepresented in medical research should be provided appropriate access to participation in research.*)

There isn’t systematic study of history of medical research

- Scandals have been acting often as a driving force of research ethics;
- Sometimes history of research ethics has been presented as description and backwards analysis of bad cases and shocking medical experiemntations.

Pre-Nuremberg regulations of human research in Germany I

- In 1900 Prussian minister for religious, educational, and medical affairs issued a directive to all hospitals and clinics that **non-therapeutic medical interventions** are not allowed in case of minors and incompetency for other reasons or without **unambiguous consent** of potential participants; medical director is **responsible** for a study in an institution; circumstances of study performance should be **documented** in medical history research subjects.

Pre-Nuremberg regulations of human research in Germany II

- Circular of the Reich Minister of the Interior : Guidelines for new therapy and human experimentation (1931);
- These guidelines contained numerous important and currently valid research ethics principles, including consent requirement, special attention to some social groups, responsibility for research etc.
- The guidelines remained in force until 1945, but weren’t followed by Nazi doctors.

Crazy cruel experiments in Nazi concentration camps

Between 1939 and 1945, at least 70 medical research projects involving cruel and often lethal experimentation on human subjects were conducted in Nazi concentration camps. These projects were carried out by established institutions within the Third Reich and fell into three areas: **research aimed at improving the survival and rescue of German troops**; **testing of medical procedures and pharmaceuticals**; and **experiments that sought to confirm Nazi racial ideology**. More than **7000 victims** of such medical experiments have been documented. Victims include Jews, Poles, Roma (Gypsies), political prisoners, Soviet prisoners of war, homosexuals, and Catholic priests.

http://www.ushmm.org/research/library/bibliography/?lang=en&content=medical_experiments

The Nuremberg Doctors' Trial

- 25.10 1946 – 20.08.1947, **23 defendants**, including eminent German professors of medicine and high ranking public servants;
- **1750 victims** identified in the indictment;
- **The verdict** –
  - death (W. Brack, Carl Brandt, Rudolf Brandt, K. Gebhardt, W. Hoven, J. Mrugovsky, W. Sievers)
  - Life imprisonment (F. Fischer, K. Genzken, Z. Handloser, G. Rose, O. Schroeder)
  - 20, 15, 10 years, (4 defendants),Innocent (7 defendants)

Types of Nazi doctors' experiments

- Experiments on twins
- Bone, muscle, and nerve transplantation experiments
- Head injury experiments
- Freezing experiments
- Experiments on malaria and other infections
- Mustard gas experiments
- Sulfonamide experiments
- Sea water experiments
- Sterilization experiments
- Experiments with poisons
- Incendiary bomb experiments
- High altitude experiments

Resources on Doctors' Trial

- Doctors' Trial transcripts http://nuremberg.law.harvard.edu/NurTranscript/TranscriptSearches/tran_about.php
- United States Holocaust Memorial Museum on the Doctors' Trial.

http://www.ushmm.org/research/doctors/index.html

- Nuremberg Code http://ohsr.od.nih.gov/guidelines/nuremberg.html

The Nuremberg Code (1947)

- The Code was prepared and issued during Doctors' Trial to establish some general standards for human research;
- Drs Leo Alexander and Alexander Ivy prepared independently initial list of basic principles of ethical human research;

Alexander Ivy: Ethical principles for human research (1947)

1. Consent of the human subject must be obtained. All subjects must have been volunteers in the absence of coercion in any form. Before volunteering the subjects have been informed of the hazards, if any.
2. The experiment to be performed must be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease under study that the anticipated results will justify the performance of the experiment. That is, the experiment must be such as to yield results for the good of society unprocurable by other methods of study and must not be random and unnecessary in nature.
3. The experiment must be conducted (a) only by scientifically qualified persons, and (b) so as to avoid all unnecessary physical and mental suffering and injury, and (c) so, that, on the basis of the results of previous adequate animal experimentation, there is no *a priori* reason to believe that death or disabling injury will occur.

Structure of 10 principles of Nuremberg Code

- Personal autonomy of research subjects and voluntary informed consent – 1, 9
- Justification of research – 2, 3
- Analysis and prevention of risks – 4, 5, 6, 7
- Qualification, autonomy and responsibility of researchers – 8, 10, 1

The Nuremberg Code (1947)

10 important principles to biomedical research on human subjects

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, over-reaching, 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 reasonable 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.

The Nuremberg Code (1947)

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.
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.

The Nuremberg Code (1947)

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

The Nuremberg Code (1947)

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.
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.

The Nuremberg Code (1947)

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.

Human researh under influence of politics and social interests

- Some social interests were primary and individual members of society should must obey to them;
- Human research in totalitarian societies – no or very few rights for people, if they became enemies and were excluded from normal civil life : **Nazi concentration camps experiments**; experiments in Japanese **Unit 731** (head Shiro Ishii); **poison labs of the Soviet secret services** (heads Ignatii Kazakov , Grigory Mairanovsky);
- Bad cases of human research in army, prisons, medical facilities in Western countries where research subjects were subordinated people in those institutions.

UN Universal Declaration of Human Rights (1948)

- An important result of WWII was also apperance ja realization of human rights issue;
- Many important documents of modern bioethics stress the role and importance of human rights, e.g.
- CoE **Oviedo Convention** or Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine (1997) and
- UNESCO Universal Declaration on Bioethics and Human Rights (2005).

UN Universal Declaration of Human Rights (1948)

Article 2. Everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status. Furthermore, no distinction shall be made on the basis of the political, jurisdictional or international status of the country or territory to which a person belongs, whether it be independent, trust, non-self-governing or under any other limitation of sovereignty.

Article 3. Everyone has the right to life, liberty and security of person.

Article 5. No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.

Biological warfare

- Deliberate use of disease-causing biological agents such as bacteria, viruses, fungi, or biological toxins, to kill or incapacitate humans, animals or plants as an act of war;
- In the history has been many attempts to develop and use biological weapons; biomedical research is very much needed to get these;
- The Biological Weapons Convention to ban them was opened for signatures only in 1972 and entered into force 1975.

Confessions about unethical human research in Western countries – influential whistleblowers of 1960s

Henry K. Beecher (1904-1976), US

Maurice H. Pappworth (1910-1994), UK

The New England
Journal of Medicine

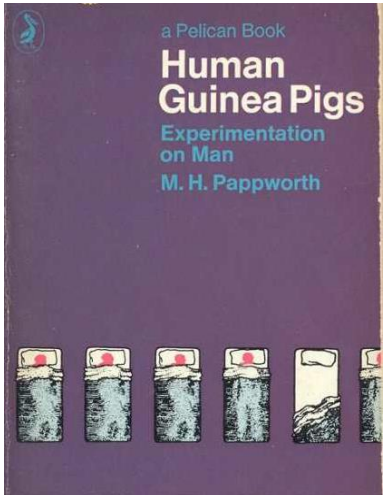
Volume 274 JUNE 16, 1966 Number 24

Reprinted from pages 1354–1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†



HK Beecher on research motivation

"Every young man knows that we will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator. If the ready availability of money for conducting research is added to this fact, one can see how great the pressures are on ambitious young physicians." (pp. 367-368)

Shocking research led by US researchers

- **Tuskegee syphilis study (1932–72)** was conducted by US Public Health Service with general goal to study the natural course of untreated syphilis among poor rural black men. Initially 600 men were enrolled into study without informed consent and later on they didn't get effective treatment with penicillin;
- In 2010 prof Susan Reverby informed the public that in **1946–48 US Public Health Service led experimental program in Guatemala** where doctors infected soldiers, prostitutes, prisoners and mental patients (1500 research subjects) with syphilis and other sexually transmitted diseases and treated most subjects with antibiotics;
- Dr **John C Cutler** was the key figure in both studies, but wasn't punished or criticized in his lifetime for these actions.

Methodological requirements have pressure on medical research and research ethics

- **NB! Bad science is unethical!**
- History of early clinical trials is quite heterogeneous, e.g. Lind' scurvy study (1753), Rush report on treatment of yellow fever by bleeding (1794), etc
- Blinding was propbably first time used in common cold vaccine study by Ferguson et al. in 1927.
- In truly modern sense the first clinical trial with properly randomized control group was performed by British MRC in 1948 to study streptomycin treatment of tuberculosis;
- In 1950s sir Austin Bradford Hill contributed strongly the methodology of clinical trials, incl. study design and statistical analysis of data.

Evidence based medicine and research ethics

- There are different levels of evidence in modern medicine, **randomized controlled trials** (RCTs) are the golden standard of EBM;
- Study design requirements (e.g. randomization, blinding, placebo control, number of participants) may produce also ethical problems which should to be solved when study is performed;
- Evidence based medicine is very resource demanding activity.

International guidelines for medical research

- WMA Declaration of Helsinki, 1964–2013
- CIOMS international ethical guidelines for biomedical research involving human subjects, 1982, 2002
- The ICH-GCP Guidelines for Clinical Trials, 1997
- Oviedo convention (1997) and its additional protocol on biomedical research (2005)

Legal regulations of biomedical research

- In some countries since 1970s medical research become regulated by some general law; e.g. in US National Research Act (1974) or Code of Federal Regulations 45.46 Protection of Human Subjects (2009), Lithuanian Law on Ethics of Biomedical Research (2000);
- Many countries have legal regulations how to manage (also how to study) medicinal products;
- Some researchers prefer clear legal regulation to declarations of research ethics.

RECs – Research ethics committees

- Since 1970s biomedical human research is controlled also by research ethics committees;
- Only through few decades RECs have undergone fast development from single sporadic institutions to systems or networks of RECs;
- WMA Declaration of Helsinki (2013)

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins….

Drug development by pharmaceutical industry or big conflicts of interests

- During last decades of 20th century drug development shifted from academic institutions to pharmaceutical industry which is in turn mainly managed by “logic of business”;
- In 1960s after thalidomide tragedy registration of new medicines became much stronger and more (safety) research were needed.

Co-operation of academic research and industry

- Research is very expensive and demands huge resources, but need for it is permanently increasing. This global situation is good soil for different problems of justice in modern medical research;
- Different conflicts of interest on personal and social level seem to turn sharper;
- A deficit with research subjects may influence their autonomy issue.
- Both international cooperation and division of labour are widely used in modern medical research.

Concepts and theories of research ethics

- Academic research on ethics in research started in 1970s;
- Specific concepts and theories for research ethics were created and developed further; e.g. general ethical principles for research, therapeutic misconseption, clinical equipoise, analysis of risks and benefits, vulnerability, inducement etc.
- Research ethics is a fruitful example of interdisciplinarity collaboration.

New areas and challenges

- Proper **balance** between personal virtous attitude (and responsible conduct) of researchers and social regulations of medical research would be an ideal to achieve;
- As research offers new themes and challenges to intervene more and more deeply into natural course of human existence, e.g. issues of stem cells, cloning, gene and tissue engineering, reproductive technologies etc., then new problems appear in addition to the existing ones.

Research ethics in CEE countries

- Both Soviet type social order and paternalistic attitude in clinical medicine didn't support open discussion on ehtical issues in medical research;
- Research ethics in CEE has been mostly **import** of principles and practices of global research ethics;
- Processes and phenomena of **transition** have been the case also in biomedical human research, e.g. role tension between doctors' double role of being local physician and researcher in big pharma sponsored clinical trial.

Conclusions

- Despite of the short history as a special field, issues of biomedical research ethics have had in medicine deep roots, influential cases and altogether longer development.
- Scientific research and its ethics are more and more controlled by society due to lack of trust between society and researchers;
- Research ethics becomes more independent field of medical ethics with its own content and formats.