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BASICS OF BIOETHICS AND BIOSAFETY

for English-speaking students of specialty 222 «Medicine»
Lecture notes

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Lecture notes
for English-speaking students
of specialty 222 «Medicine»
all forms of training

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1.1 Biomedical ethics: subject, objectives and tasks

Bioethics is a product of civilization at the end of the twentieth century. Its origin is directly related to the intensive development of biomedical knowledge. Hardly be denied that the line of the late nineteenth – early twentieth century was no less rich in discoveries and achievements, than the end of the twentieth century. Nevertheless, changes in medicine were taking a completely new character it the second half of the twentieth century. Modern medicine has a real opportunity to "give" life (in vitro fertilization), to determine and change its qualitative parameters (genetic engineering, transsexual surgery), push the "time" of death (intensive care, transplantation, gerontology).

Thus, the subject, the objectives and tasks of bioethics may be as follows.

Subject: the morality of human behavior in biological and medical industry and in health care with respect to its compliance with good morals and values.

Permission of medical interventions in the human body in terms of law, in particular, those interventions are associated with the development of the biological and medical sciences. Use of biological sciences in the service of man in order to improve living conditions.

Goals and objectives:

a) protection of human rights;
b) transplantation of organs and tissues;
c) the use of embryonic stem cells;

d) gene therapy, genetic engineering;

e) euthanasia, reproductive technologies and abortion;

f) cloning (reproductive and therapeutic);

g) clinical trials of new drugs and medical devices in humans and in animal experiments;

h) providing assistance to dying patients (hospices, providing palliative care);

i) the use of transgenic organisms in food purpose;

j) application of nanotechnologies;

k) biosecurity and biosafety.

In a narrow sense, the concept of **Bioethics** refers to the full range of ethical issues in the doctor–patient interaction. Ambiguous situations are constantly arising in the practice of medicine as a product of the progress of biological science and medical knowledge, require constant discussion in the medical community and among the general public.

In a broad sense, the term **Bioethics** refers to the study of bioethics social, environmental, health and socio-legal problems concerning not only the person but also any living organisms included in the ecosystem surrounding the man. In this sense, bioethics is a philosophical orientation, evaluates the results of the development of new technologies and ideas in medicine and biology in general.

The term "bioethics" was introduced by the German theologian ***Frets Yakhroma*** *in the article "Bioethics: a review of the ethical relationship between man and animals and plants" in 1927.*

The founder of the bioethics is an American biologist and biochemist researcher-humanist ***Van Ranseler Potter*** (1911–2001), who in the early 70-ies of XX century introduced the term "bioethics" into scientific use and defined its main focus. For many years he worked, firstly, as professor of oncology and then he was a Deputy Director of the McArdle Laboratory at the University of Wisconsin (Madison, the USA). In the 50s he was one of the first who showed a positive therapeutic effect of the combination of inhibitors of cell growth and chemotherapy in the treatment of cancer.

V. R. Potter becomes a worthy disciple and successor of the ideas of *O. Leopold* US Environmental School (1887–1948) – the

famous American environmentalist, writer and public figure. At the time, Leopold created a special ethics – ethics of land and distributed its effects not only on individuals, but on all species and ecological communities.

The history of bioethics is marked by a number of "high-profile" events related to the introduction of new medical technologies, the negative consequences of which culminated in the late 60-ies of XX century in the shares of public protest in Western Europe and America against the medicine and science. There was a question about the reliability of the protection of mankind from the "mistakes" of medical and biological science, from the application of science to the detriment of the people.

This was preceded by several violations of ethical and moral principles. In the postwar period, Nuremberg process that took place revealed the horror of the Nazi concentration camps in 1945–1946, scene of the most brutal crimes that were carried out on prisoners of war and civilians on the orders of the Nazi regime with the complicity of doctors.

"Pharmaceutical tragedy" took place in the years 1958–1961 in Germany: the mothers who took the drug thalidomide as a hypnotic during pregnancy, born about 20 thousand children with mutilations.

The World Medical Association has sounded the alarm, and the declaration was adopted at Helsinki in 1964 (additions were made in 1973, 1983, 1989, 1996, 2000). This declaration was the first international ethical standard for carrying out human research studies. The *Helsinki Declaration* "on the implementation of the recommendations of doctors in biomedical research involving humans as guinea pigs" emphasized the need for maximizing the requirements for testing on human.

1.2 Medical ethics history

Medical ethics history is divided into five stages. The short characteristic of each one is presented below.

Stage I of the Medical Ethics (8–3 thousand years BC – V–IV century BC (Hippocratic Oath))

During the Neolithic (New Stone Age, approx. 8–3 thousand BC) the system of scientific knowledge was created, which later would be called medicine. At the same time, the first stage of development of the science of the regulation of human behavior owns the art of healing, that is medical ethics.

During the first stage of development of medical ethics there emerged:

The first laws:

1) "Helping the sick is the good, the refusal (without any good reasons) is evil".

2) "Do No Harm".

3) "Thou shalt not kill" ("Don't kill").

The fundamental principles of medical ethics:

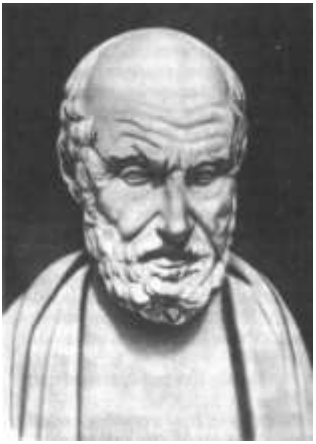
– justice;
– beneficence;
– do no harm.

A special contribution to the development of medical ethics at the first stage was made by:

1) Socrates (469–399 BC);
2) Aristotle (384–322 BC);
3) Hippocrates of Cos Great (460–377 BC).

"The first stage of the formation of the moral code of people who chose healing as a form of professional activity started with "emerging medicine" and ended with the appearance of the works of the Greek philosophers." M. J. Yarovinsky (2001).

One of the oldest medical and ethical document is the "Hippocratic Oath". This oath was given by the famous school graduates Asclepiadae whose ancestor was considered the god of medicine, Asclepius. The most famous of its graduate was famous Hippocrates of Cos Great.



Hippocrates of Cos Great
(460–377 BC)

The oath is a document sanctifying life medical schools of Hippocrates medicine. At that time there were already medical schools gluttony (corporations) doctors. Moving into the medical corporation doctors should behave accordingly: to refrain from any reprehensible actions and not to drop their dignity. The appearance of the Hippocratic oath was caused by the need to dissociate themselves from the single doctors, various charlatans and to ensure public confidence in doctors to a particular school.

The basic principle in the "Hippocratic model" of biomedical ethics is the rule "do no harm".

Thus, the first stage in the formation of the moral code of people who chose healing kind of professional activity, starting with the "emerging medicine", concluded the advent of the works of Greek philosophers, especially the works of "Corps of Hippocrates".

By M. J. Yarovinsky "Medical Ethics" (2001).

Stage II of Medical Ethics development is the emergence of monotheistic religions

Beginning of the second stage of medical ethics is associated with the approval of the monotheistic religions.

Buddhism

The ethical principle of Buddhism is desire to do good.

"Brothers, you have no father, no mother and no one to take care of you. If you do not take care of each other, then who else will? Brothers who honor me, but almost painful" – Buddha's appeal to the monks. Legend has it that an order was given after Buddha, bypassing the monks' cells, found one of them severely suffering from dysentery, weakened by illness, lying in his own feces. He picked him up, washed from head to foot, put him to bed quietly and comfortably, and then announced that the compassion and care to the patient are the most

important rules of behavior of members of the community. Since then, the monks began to study medicine, to treat each other and the laity.

Christianity

There is a tradition that Jesus was a young man who studied medical manuscripts for healing physical and mental ailments.

Heal the sick – Christ teaches his disciples (Lk 10, 9.).

According to the Holy Tradition, one of the disciples of Christ, An. Luke was a doctor. Healing is a profession Martyrs: Cosmas and Damian, Rome, the Great Martyr; Panteleimon the Healer. In the history of the Church there are many examples of priests and even bishops who were engaged in doctoring not only spiritual, but also bodily ailments.

So, for example, in the Catholic fresco of the 15th century (Mark Cathedral, Florence, Italy) "transplantology" operation is shown – Saints Cosmas and Damian sew the legs of a recently deceased person to the body of the deacon Justinian.

With the establishment of Christianity as the state, the dominant religion in Europe, Christian church took over the care and care for the sick and infirm. This duty lay on deacons.

The first known science experience of artificial insemination was carried out in 1780 in a Catholic monastery by abbot L. Spallanzani.

An Austrian monk G. Mendel became the founder of genetics.

With the approval of the knightly orders, some of them dedicated themselves to caring for the sick. For example, members of the Order of St. Lazarus of Jerusalem cared for lepers. From the name of the Order of St. Lazarus there appeared the word hospital.

In the old Russian state after the adoption of Christianity in monasteries there were set up wards.

Islam

The works of the Arab Muslim medical scientists of Central Asian Renaissance era have left a noticeable trace in the history of medical ethics.

"Practical medical ethics" by Al Ruhavi, "Order of Medicine" by Ibn Abu Useybi, "Canon of Medicine" and "Firuznoma"

by Ibn Sina (Avicenna). Many excerpts from them have become aphorisms, translated into Latin and European languages.

Carriers of medical knowledge – the priests and their assistants, helping the sick person, acting in accordance with religious regulations. It was until the medical profession became self-reliant and more common, thanks to the creation of the medical faculties of universities.

Stage III of Medical Ethics development. Creation of medical faculties at universities and corporations in the union of doctors

Medical School of Salerno was founded in the 10th century, which flourished in the 12th century and translated medical books from Arabic into Latin. It was a secular school, not a church. Its main merit was the creation of a new medical literature. The course comprised 3 years of philosophy, 5 years of medicine, 1 year of practice exam, after receiving the license. It was the first faculty of the East. Later it began to open universities in Europe.

Creation of medical faculties at universities and medical association in the corporation can be considered the end of the second and beginning of the third stage of medical ethics development.

The first university in Russia, Moscow University, was opened in 1755. Faculty of Medicine started in 1758.

The works of Dean of the Faculty of Medicine of Moscow State University M. J. Mudrov played a major role in the development of medical ethics in Russia.

Graduates of medical schools were given the so-called promise of faculty, the text of which was usually an option vow.

In the early 19th century English physician T. Percival of Manchester in the book "Medical Ethics" laid out "a set of established rules and instructions in relation to the behavior of physicians and surgeons in hospitals and private practice in relation to pharmacists, in the event that the law requires knowledge" (1803).

In the preface, Percival indicates that the job would be called "medical jurisprudence", but realized that it was wrong, because the laws had not yet been written for all occasions, encountered in medical practice. Yes, and how to write laws for the cases when the Chief Justice is conscience or opinion of colleagues.

Works of T. Percival and M. J. Mudrov summarize the third stage of development of medical ethics.

Stage IV of Medical Ethics development. Deontological stage

Deontology (from Greek *deontos* is Granted and *logos* is teaching) is the ethics section, which deals with debt problems and moral requirements. **The term "deontology"** was introduced by the English philosopher *Jeremy Bentham*, who used it to refer to the doctrine of morality in general.

From the standpoint of medical ethics deontological theory of German philosopher *Immanuel Kant* (the second half of the 18th century), which he called the **"categorical imperative"** has the greatest interest. "Act so that the maxim of your will at any time can become a principle of universal legislation".

In this self-constraint a person finds true freedom, and finds true human dignity (as the realization in his person the dignity of all humanity). Kant voiced in his categorical imperative "golden rule", generally accepted in the name of ethics of the biblical commandment: "Do unto others as you would have them do unto you".

Obviously, the most important principle of modern biomedical ethics – respect for the moral autonomy of the patient – it goes back to the Kant's conception of moral freedom, responsibility and dignity.

Stage V of Medical Ethics development (from 70th years of XX century) is Bioethics.

Bioethics is the systematic study of human behavior (not just medical) in the life sciences and health care to the extent that this behavior is considered in the light of moral values and principles of the "Encyclopedia of Bioethics".

Van Rensselaer Potter examines bioethics as a "new discipline" which is the bridge thrown to the exact sciences and the humanities, or to be more precise, a bridge between biology and ethics, hence the "bioethics".

1969 – the formation of a research center in the field of bioethics – the Institute of Society, Ethics and Life Sciences (Hastings Center, New York).

1971 – the formation of the Institute for Ethics named by Kennedy at Georgetown University (Washington).

1972 – the publication of the Bill of Rights of Patients American Association of hospitals.

1974–1978 – organization of the National Commission for the Protection of man as the subject of biomedical and behavioral research.

1978 – exit the "Encyclopedia of Bioethics" (4 volumes).

1980 – the creation of the Presidential Commission for the Study of Ethical Problems in Medicine and the behavioral sciences.

1.3 Main bioethical theories and principles

The principle of "do no harm" (Hippocratic model)

This principle was proclaimed by Hippocrates and recorded in his "Oath". Obligation "to refrain from causing any harm" has become since the time of Hippocrates not only the main moral principle of medical practice, but also the moral basis of the model of interaction of health care workers to patients, their families, their peers and teachers. The "Hippocratic Oath" includes all areas of the doctor, in which he must follow the principle of "do no harm": the physical (properly treated, choose the method of treatment, which will bring the least harmful side effects, do not accelerate death and abortion), socio-psychological and legal (non-disclosure of medical confidentiality), moral (respect and gratitude to my teachers, colleagues).

At the present time there are the following **forms of harm** that may be caused by the patient:

1. The damage caused by failure to act, failure to assist someone who needs it. This type of injury is among the most serious misdemeanors health worker and entails not only a moral judgment, but also administrative sanctions, and in some cases, criminal penalties.

2. Damage caused by negligence or malicious intent, such as an ax to grind. Depending on the consequences for the patient this kind of damage can also lead to all kinds of punishment.

3. Damage caused by improper, reckless or unskilled Business Plan. This is the damage that is the result of professional medical personnel errors. Depending on the degree of harm caused it entails a different kind of punishment.

4. Damage caused by objectively necessary actions in this situation. The only form of harm that is caused almost always, but in varying degrees. This damage, which for causing a health worker carries no penalties.

The first three kinds indicate the health worker professional incompetence and varying degrees of his morality deformation.

The principle of "do good" (model Paracelsus)

The principle of "do good" declares the moral norm perform actions for the benefit of the patient. This principle was first formulated by Paracelsus. The basis of this ethical principle of medicine made the ideas of Christianity that love of neighbors should be manifested in good works for them.

"Model of Paracelsus" is a form of interaction between health care worker with the patient and his family, in which the moral relationship between them is one of the main elements of the therapy. In the model of Paracelsus leading importance is given to the individual personality characteristics of the patient and the establishment of trust between the doctor (and other health care professionals) and the patient.

The principle of "respect for duty" (deontological model)

Entered the medical ethics together with the doctrine of professional duty medical care workers. According to this principle, the provider must comply strictly with the prescribed medical ethics rules and regulations and in accordance with them their professional duties. Requirements of professional duty are strictly for performance.

In accordance with this principle, for the health care worker it becomes a professional duty to follow the principles of "do no harm", "do good" and other ethical principles and standards. Violation of the requirements of professional duty entails certain penalties (moral, administrative, legal).

The principle of respect for human rights and dignity (bioethics)

Bioethics is leading, as it allows to the greatest degree to realize the rights of the patients in relation to their life and health.

Respect for the rights and dignity of the patient is shown in following four ethical rules: **justice**, **veracity**, **confidentiality and informed consent**.

The main point is that the subject of biomedical ethics primarily quickly accumulates new achievements, and their in-depth study to determine the degree of danger in the present and future in their application to mankind and society as a whole. (President of the Academy of Medical Sciences, Acad. RAMS VI Pokrovsky 1997).

American bioethicist Robert Veatch distinguishes four *models of relationship* between a health care worker (physician) and a patient, existing in modern medicine:

a) collegial;
b) contract;
c) engineering;
d) pastoral (paternalistic).

There are following *principles* of biomedical ethics:

a) respect for autonomy;
b) nonmaleficence;
c) beneficence;
d) justice.

Rules of bioethics: veracity, privacy, confidentiality, fidelity, freedom of will and choice, informed consent.

Autonomy is understood as a form of personal freedom, in which the individual performs actions in accordance with the freely chosen by the decision.

Term "autonomy" includes seven main aspects:

1) respect for the individual patient;
2) provision of psychological support in difficult situations;
3) giving him the necessary information (about the state of health and medical measures proposed);
4) choice of the alternate embodiment;
5) patient autonomy in decision-making;
6) ability to monitor the progress of the research and treatment (by the patient);
7) the involvement of the patient in the process of medical attention ("therapeutic partnership").

Paternalism is traditionally prevailed in medical practice, giving way to the principle of cooperation. Moral value of autonomy has been so high that the doctor's deed contrary to the will and desire of the patient was considered to be unacceptable. The American Hospital Association had been actively discussing patients' rights and approved a bill on the rights of patients in late 1972. The patient's right to autonomy was first formalized. Paramount right to the information necessary for informed consent was patients' rights, adopted by the American Hospital Association.

Informed consent is a voluntary patient's acceptance of treatment or therapeutic procedures after providing adequate medical information.

Informed consent can be divided into two stages:

1. Provision of information.
2. Obtaining consent.

Stage 1. Provision of information includes the notion of voluntariness and competence. The doctor must inform the patient about:

– nature and purpose of the proposed treatment;

– an associated significant risk; i. e. physician should affect the four aspects of risk: its nature, severity, probability of its materialization and surprise of its materialization;

– possible alternative to this kind of treatment (doctor gives advice about the most appropriate form from a medical point of view, but the final decision is made by the patient).

Stage 2. Obtaining consent. Informed consent implies the non-use by physicians of coercion, deception, threats in decision-making by the patient.

Two moral theories: ***deontological and utilitarian*** dominate in the field of medical ethics.

Utilitarian theory of morality is based on the belief that the criterion of human actions is useful (J. Bentham).

Medical ethics is a set of regulatory principles and norms of behavior of health workers (doctors) due to their specific activities, position and the role that has been ascribed to them in the society.

Medical deontology is the doctrine of the principles of proper medical activities.

Medical deontology is more inclusive concept than medical ethics, since it includes not only moral and ethical aspects of medical care, but also actions of the organization, improving knowledge, skills.

Medical deontology includes the following sections of specific knowledge:

– relationship between the doctor (medical officer) with the society and the state;

– principles of behavior, relationships and actions of the doctor (medical officer) in relation to the patient and the people around him, especially to close relatives;

– the relationship between a doctor and medical staff.

Confidentiality rules in terms of specialization and computerization of medicine:

1. Rules of the case histories.

2. Privacy and communication with relatives of the patient.

3. Anonymity of medical information in scientific demonstrations and publications.

4. Responsibility for violation of the principle of medical confidentiality.

5. Possible confidentiality restrictions.

Rules of ***veracity***:

1. Right, duty, the possibility and expediency always be truthful in the doctor–patient relationship.

2. Veracity and incurable patients.

3. "Holy lie" (adapted true).

4. Placebo.

5. Patient's right to receive truthful information.

1.4 Communication between healthcare professionals and patients

There are the following types of communication:

1. "*Contact masks"* is a formal communication, when there is no desire to understand and take into account the personal characteristics of the interlocutor, familiar masks are used (courtesy, modesty,

compassion, etc.) – a set of facial expressions, gestures, standard phrases that hide true emotions, attitude to the interlocutor.

As part of the diagnostic and therapeutic interaction this kind of communication is evident in the cases of low medical or patient's interest in the results of interaction.

2. *Primitive communication* is evaluating another person as desired or interfering object if needed – that actively come into contact if interfere – "push".

Such kind of communication can occur within the manipulative communication healthcare professionals and patients in cases where the aim of the treatment becomes to receive any dividend (sick leave certificates, formal expert opinion, etc.). Formation of a primitive form of communication can take place at the request of a medical worker in cases where the patient is a man, which may depend on his well-being. Interest to the contact member in such cases disappears, followed by obtaining the desired result.

3. *Business communication* is communication that takes into account peculiarities of personality, character, age, mood of interlocutor with focus on the interests of the case and not on the possible personality differences.

4. *Spiritual interpersonal communication* is rare in the system (medical officer) doctor – patient. It implies the opportunity to raise any topic in the conversation, share any intimate challenge of each participant of communication.

Diagnostic and therapeutic interaction does not imply such intimate contact, at least, does not provide for reasons of professional orientation confession health worker.

5. *Manipulative communication* aimed at capitalizing on the interlocutor with the use of special techniques.

The objective of such manipulation can be:

a) reduction of the patient's expectations of treatment success in connection with the avoidance of medical professional liability in the event of a sudden deterioration in the patient's health;

b) demonstration of the need for additional actions on the part of qualified health care professional in order to obtain compensation.

Types of communicative tolerance: intellectual, value–orientation, aesthetic, ethics, emotional, sensory, algorithmic, characterological, functional.

Intellectual tolerance transmits paradigm (model, type, style) of mental activity of a particular person, that is, the principles of his understanding of reality, familiar to him stereotypes of understanding issues, ideas, decision-making.

Value-orientation includes basic philosophical ideals of a particular person, his life coming and/or long-term goals, interests, assessing the situation.

Aesthetic covers an area of preferences, tastes and feelings.

Ethics expresses the moral norms, which are followed by people.

Emotional reflects the emotional state of the most characteristic for the person (joy or sadness, excitement or serenity, the rise or depression, anxiety or carelessness, peacefulness or aggressiveness, optimism or pessimism).

Sensory characteristics include sensory perception of the world at the level of visual, auditory, olfactory, gustatory, cutaneous and motor sensations.

Algorithmic – this substructure personality combines personal qualities that ensure uniformity of reproducibility. These are habits, skills, style of activity, different rituals, including household, family, religion.

Characterological includes stable type of forming personality traits, congenital or acquired under the influence of the environment.

Functional includes requirements and emerging on the basis of their preferences and desires.

Models of healing can be divided into the following types.

1. Model of "technical" type.

One consequence of the biological revolution is the emergence of a physician-scientist. Scientific tradition prescribes scientist "to be impartial". He must rely on the facts, avoiding value judgments. Only after the creation of the atomic bomb and the Nazi medical research, when a test is not recognized nor any rights (experiments conducted on prisoners of concentration camps), mankind has realized the danger of such a position. A scientist cannot be higher than the human values.

The doctor in the decision making process cannot avoid moral judgments and other valuable character.

2. Sacred type model.

The basic moral principle that expresses the tradition of sacred type says "providing patient care, do not cause him any harm". Benefit and not to cause harm. No doctor can perform a moral duty to benefit and thus completely avoid injury. This principle exists in a broader context and is only one element of the whole set of moral duties.

3. Collegial type model.

The purpose of medical practice is the elimination of the disease and protects the health of the patient. In the model of collegial type trust plays a crucial role. However, ethnic, class, economic and value differences between people make the principle of common interests that are necessary for the collegial model unwieldy.

4. Contract type model.

Model of social relations that most closely matches the real conditions, as well as the principles of bioethics, historical model is a model based on the contract or agreement. The agreement assumes the principles of freedom, personal dignity, honesty, fulfillment of the promises and justice. This model avoids the rejection of morality on the part of the doctor.

Questions for Self-checking

1. What is Bioethics?
2. Who coined the term "bioethics"?
3. Describe main stages in history of the biomedical ethics development.
4. Describe main aspects of "Hippocratic Oath".
5. What is the basic moral principle of bioethics?
6. What is Deontology?
7. What are the main principles and rules of biomedical ethics?
8. List and describe types of communication between healthcare professionals and patients.
9. What work belongs to V. R. Potter?
10. What scientist coined the term "ethics"?
11. Describe an informed consent.

Topic 2. Bioethical problems of life, dying, death and resuscitation. Medical, ethical and legal problems of genetic reproductive technologies

Main lecture questions:

2.1 Family planning and abortion

2.2 Euthanasia: ethical and legal issues

2.3 Transplantology

2.4 Genetic reproductive technologies: ethicality and legality

2.1 Family planning and abortion

Family planning is an activity that helps individuals and couples achieve certain reproductive outcomes: to prevent unwanted pregnancy, birth of children desired, adjust the intervals between pregnancies, to control the timing of birth, depending on the age of the parents, and other factors to determine the number of children in family. This includes information on how to achieve these goals, providing an informed choice, the opportunity to use the full range of safe and effective methods of contraception.

Family planning can include a range of activities, from the planning childbirth, infertility treatment and finishing with sex education, counseling on family life, including genetic counseling. However, the need to clarify the fact that none of the existing methods for today prevent an unwanted pregnancy cannot be considered ideal for all situations in life and cannot be acceptable to all cultures, religions and social conditions.

Abortion, contraception and sterilization are a modern form of medical intervention in human reproduction.

For the first time population growth was seriously concerned about the priest *Thomas Malthus*. In 1798, Malthus wrote his major work *"Essay on the principles of population"* (a treatise on the principles of population). According to the doctrine of Malthus, humanity is threatened by catastrophe of "absolute surplus people" because sooner or later there will not be enough food for people. Malthus calculated that the human population is growing exponentially, and the amount of food – in arithmetic. The way out of

the crisis of hunger Malthus pointed to the methods of birth control in the form of late marriages and self-control.

The beginning of the XX century was marked by the rise of birth control policies primarily in the United States. In the second decade of the XX century under the wing of the Socialist Party of America gathered almost all the extremist forces: the radical Republicans, the reformists – Unitarians, "The Knights of Labor", anarchists, populists, suffragettes, communists and others. A member of the party was Margaret Sanger – the future leader of the world's fertility and sexual revolution supervisors. In 1916, she established the *American Birth Control League*, later named *International Planned Parenthood Federation*. Her multibillion business, of course, is associated with eugenics, and later with fascism. She opened her clinics in the poor neighborhoods inhabited by Slavs and South Americans, explaining that these people "multiply rapidly". With the coming to power of the Nazi regime in Germany, its leaders began to pursue a policy of destruction of the Slavic races in the occupied territories, using the same methods and tools for reducing fertility.

The International Planned Parenthood Federation has offices in almost all countries of the world and uses the ideas developed by Margaret Sanger and the method of genocide to reduce the birth rate in countries that are developing, especially in the rich mineral and energy resources. In some of them there is a tendency for the legalization of abortion.

Now the International Planned Parenthood Federation, as well as 45 years ago, aims to implement birth control method worldwide by maens of legalization of abortion, contraception and sterilization distribution of the population. International Planned Parenthood Federation roughly despised even by international law. By convention, signed by most European countries, "the person, organization or government that uses the measures to reduce the birth rate can be charged with genocide". However, the support, the governments of countries such as the UK, Holland, the USA, enables organizations to "family planning" with impunity.

Liberal and conservative views on issues of contraception and abortion

Considering the ethical issues of abortion one cannot think of social movements against the West: the movements of ***pro-choice*** and ***pro-life***. Liberal movement *Pro-choice*, from the word "choice" refers to the right to choose abortion.

The main slogans of the movement are:

1. A woman has the right to dispose of her body, so she has the right to choose to give birth or not to give birth.
2. An embryo is not a human, not a child.
3. Every child should be desired.
4. Abortion and contraception are safe.

Conservative movement *Pro-life* appeared in the West in contrast to the Pro-choice movement. It protects the right to life from the moment of conception.

1. Embryo is not a part of the woman's body. This is the body of another person because a woman's body can dispose of at will, and others tell "Yes, life of another person shall dispose of it". After all, the main direct right is the right to life.

2. The embryo is a human being at any stage of pregnancy. This argument is an evidence of both religious (person before birth has a soul, because a spirit is able to communicate with God), and the natural sciences. From the point of view of modern biology (genetics and embryology) a person's life as of a biological individual, begins with the fusion of male and female gametes and the formation of a single nucleus, which contains the unique genetic material.

3. Other ethical issues of abortion, which always emphasize its opponents, include:

– the feeling of pain and fear in the embryo during an abortion;

– underestimation of the risk of post-abortion complications in the woman;

– psycho-emotional problems, "post-abortion syndrome";

– complications in children born to mothers who have had abortions;

– a violation of the ethical rules by the doctors of the information consents as adequately inform women about the risks and fetal maturity (even for pregnancies up to 12 weeks).

According to the concept of voluntary consent of the information, the physician must inform the patient of the consequences of any medical intervention. Medical abortion is the only surgery that is performed without a medical examination. And this is only the intervention, the outcome of which is not to improve the health of the patient, and vice versa! Human being – a child – dies, and reffer to women, which held abortion, causes significant health damage. That is, "harmless" abortion does not happen.

The doctor scrapes the uterus, the cervix is widened blindly, without seeing the surgical field and therefore there is a danger of perforation of the uterine wall by one of the tools.

The remains of the uterus fragments of the ovum may cause the development of placental polyp or accumulation of blood in the cavity of the uterus, which is an indication for re curettage of the uterine cavity.

The remains of the ovum, placental tissue, blood in the uterus are a breeding ground for microorganisms. Therefore, there is a risk of inflammation of the uterus, pelvic peritoneum, and even sepsis. These complications may occur if the vagina before abortion was inflammation during an abortion infection got into the sterile uterine cavity and then into the abdominal cavity.

Abortion can cause dysfunction of the ovaries. It's no secret that even as a result of abortion may be the only infertility. Injury of muscle fibers during an abortion may lead to the next pregnancy failure and, as a result, miscarriage and cervical dystonia.

Endometriosis is a severe complication after abortion. The normal endometrium (inner functionally active layer) lines the uterus and is torn away from each menstruation. For injuries of the uterus endometrial particles begin to "grow" into the muscle layer. This leads to the development of endometriosis. Almost half of these patients develop infertility.

Carrying out an abortion in a woman with Rh negative is a factor especially at the first pregnancy, resulting in rhesus conflict, the result of this woman's inability to bear the subsequent pregnancy.

There are also psychological effects of abortion. In our country, they are very poorly understood. Psychologists point out that post-abortion depression and feelings of guilt are developed in women, which are independent of the social environment in which the woman resides. It was also observed in non-Christian countries, such as Japan, where, after the legalization of abortion there was established children church where women could bring figurines, dolls, which symbolize their aborted children. Thus, they brought a kind of sacrifice and that was expressed repentance.

After an abortion, a woman is aware of the guilt associated with the loss of sense of her own usefulness. It should be noted, by killing a child a woman destroys something big that would be the goal of her life.

This leads to the destruction of basic trust between spouses and later, to the rupture of family relations. More often, it leads to the end of extra-marital relations.

In such cases, there is no sense of gratitude, of the familiar to the patient with respect to his surgeon after curative surgery, but instead it leads to the resentment and anger. A patient whose doctor refused to carry out an abortion would never have claim to it, but rather thank for saving a child.

How can the ethical position protect a doctor? What are the goals of medical and health activities?

To help a person overcome the disease, or at least alleviate the suffering of the patient in the case of abortion, neither one nor the other chains are not achieved because the pregnancy is not a disease. During an abortion one of the two patients is injured, we talked about (physically and mentally), and the other is dead.

For many women, it is enough to see her child on an ultrasound monitor screen and listen to the beating of its heart to abandon the abortion decision. Contrary to current thinking, the abortion rate is not related to economic factors (the link between material wellbeing of the

family and abortions cannot be traced). In contrast, in poor countries, families are large and wealthy families tend to fewer children.

Medical and ethical evaluation of abortion

The point of view of experts who are against abortions is consistent with the text of the Hippocratic Oath (V–IV century BCE), which contains the following: "I'll never give a woman an abortive means".

Let's compare domestic ethical standards with international ones. We turn to the Declaration "On the medical abortion" (adopted by the General Assembly of the World Medical Association in September 1948, supplemented by the 35th Assembly in October 1985.) The Declaration proclaims the principle "respect for human life from the moment of conception" as the basic moral principle of doctor.

The right to refuse medical abortion

Ukrainian legislation does not provide for the right of a physician to refuse abortion. Indeed the right to refuse medical "assessment and treatment" of a patient can be realized only if adhered to the following grounds.

First, such a refusal is admissible only if the patient does not comply with the orders and regulations of the therapeutic or prophylactic institutions.

Second, the failure of examination by a physician and treatment of the patient, must not threaten the patient's life and the health of others.

Obviously, the reluctance of doctors to search through a life that is born, fits into the framework outlined by the law out of "investigation and treatment of the patient". In the case of abortion, it is not about "treating" a patient and a medical intervention, the possibility of failure on the part of the doctor when is not regulated by existing provisions.

In this case, we refer to the specific regulations of the existing world. In particular, the right to refuse medical abortion is enshrined in paragraph 6 of the Declaration of the World Medical Association "The medical abortion" (Oslo, August 1983), according to which, if personal beliefs do not allow the doctor to make medical abortion, he should entrust the patient to a competent colleague.

There are different abortion laws in certain countries of the world according to the degree of severety.

The most liberal laws are envisaged in countries where abortion is permitted for a woman's request:

a) former socialist states, the Scandinavian countries (abortion is permitted in the first 3 months of pregnancy);

b) Sweden (abortion is permitted in the first 18 weeks of pregnancy);

c) Denmark (abortion is permitted in the first 21 weeks of pregnancy);

d) US (abortion is permitted in the first 24 weeks of pregnancy);

e) Tunis and Singapore (there are no restrictions to abortion).

The most severe laws are provided in countries where abortion is permitted only on a limited range of medical and genetic evidence: Belgium, Ireland, Italy, Luxembourg, Malta, Monaco, Portugal, Albania, Brazil, Colombia, El Salvador, Uruguay, Bangladesh, Indonesia, the Philippines, Algeria, Kenya, Nigeria, Morocco, New Zealand, Fiji.

The appearance of the embryo at different stages of embryonic development is presented below (fig. 2.1).

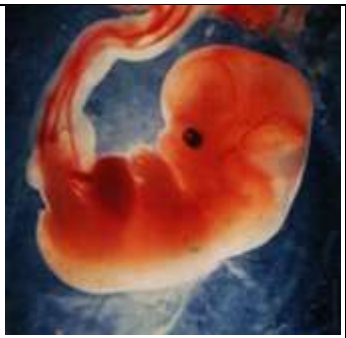
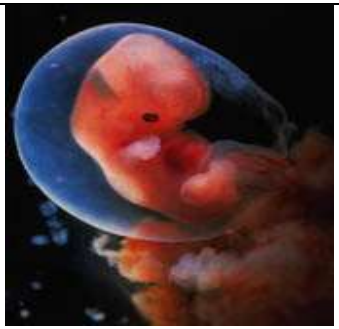
	***Five and a half weeks*** The length of the embryo is 10–12 mm. Eyes are clearly defined by dark circles. The ending has developed into a small hand. Blood with oxygen and nutrients is supplied to the embryo through the umbilical cord
	***Six weeks*** The embrio is already starting to move as much as 12 weeks earlier than the time when the mother feels the movements. Embrio's heart beats at a frequency of 140–150 beats per minute, twice as much as by mother
	***Eleven weeks*** Fetus' weight is about 30 grams, length is 6 cm. The heart starts beating at 18–25 days. The little creature can pucker, change facial expressions and even smile. All body systems are improved

Figure 2.1 – The appearance of the embryo at different stages of embryonic development

	***Twelve weeks*** Fetus is well "settled" in the uterus, brain and nervous system begin to play an important role. Three-month-old fetus is like a newcomer in the universe, "astronaut" in a special capsule with a leash, which supplies everything necessary for life and development. In most cases, the mother may serenely move
	***Sixteen weeks*** 11–15 week fetus grows every month by 5–15 cm. It already knows how to grasp something with hands, swim and even roll
	***Eighteen weeks*** The length of the fetus reaches 20 cm. Look at the handle, a true work of art. Thumb is already well developed, the fetus is able to suck it. It becomes active and energetic; straining muscles, pushes arms and legs. Now its mother feels movement

Figure 2.1, continuation

2.2 Euthanasia: ethical and legal issues

Euthanasia is an easy, painless death that occurs as a result of certain actions of man in relation to himself, or as a result of certain actions by other persons acting solely at the request of a person who by reason of his own physical disability, needs their help.

Exception: if a person, who has critically ill physical condition, doomed to a slow death, is not able to express his will, the actions of the people, who take in such a case the responsibility for decision-making in respect of such person, may also be considered euthanasia, when it was decided.

It should also be recalled that the above-mentioned exclusion is the most problematic aspect in the issue of euthanasia, and that the exception should be made for the determination of euthanasia, since the category of people who are physically unable to express their will, can not at least need to be euthanized than those who are physically able to ask for euthanasia. Category of terminally ill people experiencing physical pain and mental suffering, who are not able to know physically that they need to be euthanized, only on the basis of physical disability the right to euthanasia is denied, this means that such legislation does not protect the person, but dooms him to a slow painful death.

Problem of euthanasia begins its chronology in ancient times. And even then it caused much controversy among physicians, lawyers, sociologists, psychologists. English philosopher *Francis Bacon* (1561–1626) coined the term "euthanasia" (from Greek euthanasia, *eu* is good, *thanatos* is death) i. e. a good, quiet and easy death, without pain and suffering to refer an easy painless death.

Types of euthanasia

In theory, there are two types of euthanasia: *passive euthanasia* (the intentional termination of the patient's medical maintenance therapy) and *active euthanasia* (administering medications for dying or other actions that result in a quick and painless death). Active euthanasia is often classified as *suicide with medical assistance* (provision of the patient at the request of drugs that reduce life).

Active euthanasia is the implementation of actions to accelerate the death of a man, according to his own decision. Also active

euthanasia can be called actions of the person to accelerate his own death. For example, a special organization (and the only such organization is "Dinite" in Switzerland) provides an apparatus which is set in motion by the person in need of euthanasia.

Active euthanasia at the legislative level is only allowed in three European countries: Belgium, the Netherlands and Luxembourg. Also active euthanasia is allowed in Oregon and Washington of the USA. And in fact, euthanasia is permitted in Switzerland, that is officially euthanasia is prohibited by law, but Swiss law permits to assist in the implementation of suicide.

In addition, it is necessary to distinguish between voluntary and involuntary euthanasia.

Voluntary euthanasia is carried out at the request of the patient or a previously expressed consent (for example, in the United States a common practice in advance and in a legally valid form of expressing their will in the event of irreversible coma).

Involuntary euthanasia is carried out without the consent of the patient, as a rule, is unconscious. It is made on the basis of the decision of relatives, guardians, etc. Council on Ethics and Judicial Affairs of the American Medical Association in this case admits that these decisions may be "unfounded". However, in the case of a "competent decisions", it is believed that people have the right to make decisions that others feel foolish, because their choice of passes through the competence based process and is compatible with their personal values.

Passive euthanasia is to stop any action to sustain human life, provided that the person himself made the decision (such as turning off the respirator).

"For example, we can get the situation with the patient a hundred years ago. In the XIX century, hopelessly sick would just quietly die, giving soul to the Lord, and now he would be breathing through a respirator, heart would beat through the apparatus of the artificial heart, the kidneys have to work with the appropriate unit, etc. And outside the intensive care unit physicians would argue what to do with him then" (Prof. Gorovsky).

Passive euthanasia is permitted in more than 40 countries around the world.

The difference between active and passive euthanasia.

American philosophers, analyzing the difference between active and passive euthanasia, state: "An important difference between active and passive euthanasia is that in passive euthanasia the doctor does nothing, and the patient dies because some disease has struck him. With active euthanasia the doctor does something that leads to death of the patient, i. e., he kills him. Physician who makes a lethal injection to a cancer patient causes the death of this patient, but if it's just to stop treatment, the cause of death will be cancer".

Declaration on the treatment of terminally ill patients suffering from chronic pain

Treatment of terminally ill patients suffering from chronic pain, should be carried out so that they can die with dignity. Proper use of opioid and non-opioid analgesics may relieve the suffering of the majority of terminally ill people. Doctor and all involved in the treatment of patients suffering from the pain of the dying are obliged to adequately represent the genesis of pain a patient experiences, know the clinical pharmacology of analgesics, to understand the needs of the patient, his family and friends. The Government is obliged to ensure the availability of such a large number of opioids, which are necessary for the adequate management of severe chronic pain.

Principles of the clinical management of severe chronic pain

The physician should focus on alleviating the suffering of the terminally ill patient. The pain experienced by this patient, is only one part of his misery. The degree of pain can range from tolerable to unbearable.

There is a difference between acute and chronic pain; it dictates the use of a particular opioid analgesic. The following are the general principles of the analgesic benefit in severe chronic pain.

1. Treatment should be individualized so that both can adequately meet the needs of the patient and to maintain, as much as possible, the state of comfort.

2. It must be remembered that the tolerance of chronic pain is different from acute pain tolerance.

3. In order to rid the patient of the pain a physician must know the strength, duration and side-effects of available analgesics, choose the appropriate, to determine the dose and dosage regimen.

4. To the patients who are not helped by non-opioid analgesics, a combination of non-opioid analgesics and opioid may produce a marked effect.

5. The loss of analgesic effect because of the patient's addiction to the drug dictates replacement analgesic.

6. The emergence of iatrogenic dependence on the drug should not be seen as a major problem in the treatment of severe pain on the background of neoplastic diseases and cannot be grounds for rejection of the use of strong analgesics in patients whom analgesics may help.

Venice Declaration on Terminal state

1. During the treatment the doctor must, if possible, ease the suffering of the patient, guiding by his interests.

2. Exceptions to the above are not allowed, even in the case of incurable diseases and deformities.

3. Exceptions to the above principle, without considering the following cases:

a) the doctor does not extend the agony of the dying, stopping at his request, and if the patient is unconscious – at the request of his relatives, the treatment that can only delay the onset of the inevitable end. Refusal of treatment does not relieve the physician from the obligation to help the dying, assigning drugs to alleviate the suffering;

b) the physician must refrain from the use of non-standard methods of treatment, which, in his opinion, will not have any real benefit to the patient.

The doctor can artificially sustain the life of the deceased functions in order to preserve his organs for transplantation, provided that the country's laws do not prohibit this, there is consent given before a terminal condition by the patient, or after ascertaining the fact of death, his legal representative and death pronounced doctor right not associated with the treatment of the deceased, nor with the treatment of the intended recipient. Doctors assisting the dying, should not depend on the potential of the recipient, or by treating his doctors.

2.3 Transplantology

Transplantation is the transfer (engraftment) of human cells, tissues or organs from a donor to a recipient with the aim of restoring function(s) in the body.

There are four main types of transplantation:

1. *Autotransplantation* (autologous transplantation) – recipient of a donor graft is for himself.

2. *Izotransplantation* (homologous transplantation) – donor transplant is 100 % genetically identical to the recipient and immunologically identical twins recipient.

3. *Alotransplantation* (heterologous transplantation) – donor transplant is an organism of the same species, but genetically and immunologically different from the recipient.

4. *Xenotransplantation* (interspecies transplantation) – organ transplantation from another species than people (e. g. pets).

Although the idea of organ transplantation is an old one, successful transplantation did not occur until the twentieth century. Today the transplantation of many organs between well-matched human beings is quite successful, with the majority of recipients living five or more years. Kidney, cornea, bone marrow and skin transplants today, for example, are considered routine for certain conditions. Heart and lung or heart-lung transplants, liver and pancreas transplants are also becoming more common.

The ethical and legal issues related to organ and tissue procurement and transplantation are often discussed in light of such principles as *autonomy, benevolence, non-maleficence, free and informed consent, respecting the dignity, integrity and equality of human beings, fairness, and the common good*.

Transplants between living persons raise the question whether it can ever be ethical to mutilate one living person to benefit another. Concerning this many distinguish between parts of the body that can regenerate (e. g. blood and bone marrow) and parts that do not regenerate. Regarding the latter some are paired (e. g. kidneys, corneas and lungs), whereas others are not (e. g. heart). A competent adult can give free and informed consent to be or not to be a living donor, but an incompetent person cannot. Can a guardian ethically consent for a

legally incompetent person, such as a severely mentally disabled adult or a minor, to be a living donor? Regarding medical decisions an incompetent person's guardian is to act for their benefit or best interests, and, as far as possible, their wishes, if known and reasonable.

Ethical Issues Regarding the Recipient

Nobody (i. e. no potential recipient) has a claim on organs or tissue of any person, living or dead. The sick should thus accept the tissue and organs freely offered by others as a gift. This position is widely accepted.

Another moral issue involving the recipient is free and informed consent. A competent person who could possibly benefit from receiving a transplant should be adequately informed regarding the expected benefits, risks, burdens and costs of the transplant and aftercare, and of other possible alternatives. So should the guardian(s) of an incompetent person. A legally incompetent person who can understand some things that are relevant to their condition, a proposed transplant, and decisions that they are capable of making, should be informed of these in an appropriate way. Guardians should respect the wishes, if known and reasonable, of incompetent persons in their care. Proper safety measures should be followed to protect transplant recipients from receiving AIDS and hepatitis viruses, etc.

The main ethical issues in transplantation can be grouped into blocks:

1. **The first block** of the ethical problems is associated with the commercial relations during transplantologic operations.

2. The second block is problems related to statement of a person's death and the criteria for brain death.

3. The third block is transplantation (deletion) bodies and (or) tissue from a living donor or a cadaver.

The problem of transplantation commercialization

It is known that the purchase and sale of organs is prohibited by international and Ukrainian legislation. The prohibition of buying and selling humans also applies to the organs and tissues.

The ethical principles that limit the commercialization of transplantation, are a kind of "hurdles" in the way of possible dangers.

This is the task of the ethical principles governing the diagnosis "brain death".

Ethical issues related to ascertaining death on criteria of brain death

Historical criteria of a person's death is the lack of independent work of two body systems: respiratory and cardiovascular. Today, the traditional, historical criteria added one that is the "brain death".

The criterion of "*brain death"* was formed gradually. In 1959, French neurologists P. and M. Molar Gulon described the state of otherworldly coma, in 1968 criteria of brain death were developed at Harvard. The Declaration of Sydney have been confirmed and clarified the same year.

The concept of "brain death" is based on an understanding of a person's death: the death of a man is irreversible degradation and (or) the dysfunction of critical body systems, i. e. systems, essential artificial, biological, chemical or electronic technology systems, not just the brain is fungible.

The concept of "brain death" and "biological death" are mixed not rarely. It is important to say that, although the criterion of brain death is accepted in medicine, but in society, it clearly does not perceive. This is due to the traditional views of people about the heart as the heart of a man.

Types of Consent (Voluntary or Expressed, Family, Presumed, Required Request, Routine Inquiry)

Voluntary or expressed consent involves a person making known free offer to donate one or more of his organs and/or bodily tissue, after person has died or while alive. Concerning cadaver donation, a person can express his wishes by some form of advanced directives, such as by filling out the Universal Donor Card attached to their driver's license. ***Free and informed consent is required when the transplantation is from a living donor.*** Previously expressed voluntary consent regarding a deceased donor is the ideal because it involves an act of love and responsible stewardship over one's body. It also communicates to others, including one's family and health care professionals, one's wishes.

Many potential organs and tissues for transplantation (e. g. of brain-dead accident victims) are lost because the people did not previously express voluntary consent and their families were not approached about donating. Because of this and the shortage of organs and tissues for transplantation, some have proposed other models of consent including presumed, required request and routine inquiry, to hopefully increase the supply. Although only a minority of deceased potential donors have signed donor cards, surveys show that most people favor organ donation. Some argue that it is ethical to presume consent on their behalf, unless the person while alive gave clear indications to the contrary, since a transplant does not harm the donor after death and it can benefit others.

Required request stipulates hospitals to develop protocols to ensure that families of potential donors are actually asked to donate.

Routine inquiry requires hospitals to develop protocols to ensure that families of undeclared potential donors have the opportunity to donate, people tend to react more positively when offered a choice. Some have criticized these approaches as not allowing professional discretion.

The Law Reform Commission of Canada recommends maintaining and strengthening the present express consent model in Canada with hospitals implementing routine-inquiry protocols. These, however, are to recognize professional discretion not to ask in cases where this would clearly be inappropriate.

There are three main types of legal regulation of ***organs removal from a deceased person***:

1. Standard withdrawal.
2. The presumption of consent.
3. The principle of the presumption of dissent.

The essence of the principle of routine sampling is that the body after death becomes the property of the state. This means taking a decision to exclude bodies taken in the interests of the state's needs.

Routine removal has lost its legitimacy in modern society because, saying more precisely, there are two basic principles:

1. Presumption of consent.

2. Presumption of dissent.

Presumed consent is valid in Russia, Austria, Belgium, Spain, the Czech Republic and Hungary, and other countries.

Presumption of disagreement (or dissent) is enshrined in law of the United States, Germany, Canada, France, Portugal, the Netherlands.

The presumption of consent, also known as "supposed consent" and "model of objections". This is largely due to the fact that the principle of "***presumed consent"*** is not only positive but also has ***negative aspects:***

1. The most important condition for the realization of human rights or relatives to refuse the removal of organs is a full informing the public about the nature of their rights and the consequences of their refusal. Most people do not know the mechanisms of in vivo clearance of failure.

2. The downside of this principle is that it forces the doctor to make, in effect, acts of violence to person or property, without consent. In ethics, this is qualified as "violence".

The positive side of "presumed consent" is solely to increase the number of organ transplants. This is because the authorities confiscate organs from those who expressed no opinion on that. This principle significantly simplifies the procedure for obtaining organs for physicians, because they do not need to obtain consent from relatives.

Paired organs, such as kidneys, are generally used, or a part of an organ (liver and others) is taken.

Exclusion of organs and tissues from ***a living donor*** for a transplant is the subject to the following conditions:

– if the donors voluntarily and knowingly agreed in writing to withdraw their organs or tissues;

– if the donor is warned about possible complications to his health due to surgery for removal of organs or tissues;

– if the donor has passed a comprehensive medical examination by specialists about the possibility of withdrawal of his organs or tissues for transplantation.

Ethical Issues Regarding Allocation of Limited Resources. Criteria for Selection

Requests or the demand for human organs and tissues usually exceed what is available or the supply. Significant practical and ethical questions regarding efficiency and fairness arise as to how to distribute best these limited resources. On what basis should this person rather than that one be chosen to receive a given organ? Who should choose? These decisions are serious as they can involve results about who will live and who will die. A widely used and approved criterion of selection is to give priority to those who have a great need and are expected to benefit greatly. For example, it does not make sense to give a limited number of available organs to those who will not benefit or are expected to only live marginally longer but suffer much with the transplants, when others would benefit greatly. While this criterion is widely accepted as fair, there is much discussion about how to define and assess "benefit". Many argue that both the expected length of survival and the possibilities regarding rehabilitation should be considered.

In spite of the success of transplants, care must be taken not only if they extend life biologically, but also offer the patient a real chance for a healthy life. The new organs should add new years to life, and help to provide a new and better life.

As a last resort a choice sometimes has to be made between a transplant immediately available but with a very small chance of survival, and a long term transplant offering a greater possibility of healing.

With regard to who will likely benefit more from receiving a transplant, medical criteria such as blood and tissue typing (i. e. who is less likely to reject the transplant), and the absence of other life-threatening diseases, are used. Other factors such as the potential recipient's will to live, motivation and ability to follow post-operative

directions (e. g. taking immunosuppressants), his or her family support, and the skill of the transplant team can also be relevant to the success of a transplant.

Criteria for allocation of donor organs and (or) tissues

The fourth block of the ethical problems is associated with the early stage of the distribution of available donor organs in accordance with accepted international principles main criterion that influences the decision of the doctor. Immunological and biological data of the person who needs an organ transplant, are entered into the database, that is "waiting list". Waiting queues exist at different levels, for example, in large cities, at the regional and even national level.

On the other hand, there is a database of donor organs and immunological parameters. If the biological data of the donor organ fit to the biological parameters of the person who is in the "waiting list" this person will be the recipient and get the necessary organ because his body is most compatible to donor. This principle of distribution is considered to be the most fair and fully justified from a medical point of view, as it helps reduce the reliability of rejection of the organ.

If there are more than one suitable donor organ recipient from the list, in this case it comes into action ***the second criterion is the criterion of severity of the recipient***. Under the condition of one recipient he can expect six months or a year, and another can expect no more than a week or a month. The organ is given to those who cannot wait long.

However, how to be in a situation if two recipients of organ are almost equally suitable, and they both are in critical condition and cannot wait long? In this case, the decision is made on the basis of ***the criterion of priority (third criterion).*** The physician should consider the length of stay of the recipient in the "waiting list". *Preference is given to someone who used to be written in the "waiting list".*

In addition ***distance*** is also taken into account to these three criteria, i. e. the distance from the location of the recipient to the donor organ. Body with the smallest period for a heart transplant, about five hours. And if the time spent on overcoming the distance between the body and the recipient of more time "life" of the body, the donor organ

is given to the recipient, which is at a close distance. Consequently, the main criteria for the division of donor organs as they are of importance: *first, the main, is the degree of immunological compatibility of donor–recipient pairs, the second is the severity of the recipient, and the third is sequence.*

Additional ethical issues that arise in the allocation of donor organs and tissues. Now many candidates are denied transplants. The forecast for candidates with vascular disease are less optimistic, so these patients are not included in the list for an organ transplant.

There is a list of the basic ethical principles governing organ transplants or tissues.

1. Human organs cannot be regarded as an object of sale. Declaration of the World Medical Association declares: "The purchase and sale of human organs is strictly forbidden by the Law of Ukraine "On the transplantation of organs and (or) tissues". Health care organizations are allowed to conduct organ retrieval operations on bodies (or tissues) of a corpse, and selling is prohibited.

2. Transplant from a living donor can only be based on sacrifice to save the life of another person. This consent for organ removal is a manifestation of love and compassion.

3. A potential donor must be fully informed of the possible consequences of organ transplantation for his health.

4. Transplantation, which directly threatens the life of the donor, is not morally permissible. According to the Ukrainian law, organ removal from a living donor is permitted only if the donor is a recipient of a genetic link with the exception of cases of bone marrow transplantation.

5. An unacceptable reduction in the life of one man in particular through the refusal of life-supporting treatment to lengthen the life of another.

6. The most common practice is the removal of an organ of a newly deceased people. There should be eliminated uncertainty as to the time of death.

7. There are the following three principles of Terms and Conditions of ethically correct diagnosis of "brain death": the principle of a single approach, the principle of collegiality and the

principle of financial and organizational independence of the Brigades.

8. The priority of the division of donor organs should not be determined by the identified strengths of individual groups and special financing.

9. Three criteria are taken into account in the fission of donor organs: the immunological compatibility of donor-recipient pairs, severity and priority recipient.

2.4 Genetic reproductive technologies: ethicality and legality

Surrogacy is the term used when a woman bears a child for another woman. The usual indications for this are that the woman cannot bear the child because the uterus is absent or malformed or when a medical condition exists making pregnancy a threat to her and/or her baby's health.

Natural surrogacy is when a healthy woman with normal ovaries, tubes and uterus is inseminated with sperm from the husband of a woman who is unable to carry a baby. If the surrogate woman becomes pregnant and has the baby, then the woman who cannot have the baby and her husband with whom she was originally inseminated adopt the baby. It is unethical for Fertility Associates to assist with natural surrogacy, such as by undertaking the insemination, without prior Ethics Committee on Assisted Reproductive Technology (ECART) approval.

In vitro fertilization (IVF) surrogacy is when the woman who is unable to bear the child has normal ovaries but is still unable to bear a child, undergoes IVF hormone stimulation and egg pick-up (Oocyte pick-up – OPU), with fertilisation of the eggs by her husband's sperm. Then their embryos are transferred to the surrogate. The surrogate must be healthy, have a low risk for complications during any pregnancy that occurs and be willing, after delivery, to give the baby to the genetic parents from whose egg and sperm it was conceived.

The ethical and legal issues associated with surrogacy are not simple. The Ethics Committee on Assisted Reproductive Technology (ECART) requires Fertility Associates to make an application in one

or two stages. Considerable consultation and counselling is usually required before the application can be made. Fertility Associates is very supportive of IVF surrogacy when the woman who would carry the baby is a family member or a close personal friend of the couple who need surrogacy, especially if they have completed their family. In the sphere of surrogacy, Ukrainian legislators have proven to be far more progressive than many of their European colleagues. Today, Ukraine is one of the very few surrogacy friendly countries in Europe. Unlike other nations that limit or even ban surrogacy, in Ukraine the intended parents of child are considered to be biological parents from the moment of conception, and they are specifically named as biological parents in the birth certificate without any mentioning of surrogate mother.

Importantly, the surrogate cannot legally keep the child after the birth. On the contrary: the child is considered to legally belong to the prospective parents from the very moment of conception. In fact, in the legal history of Ukraine, there has not been a single reported case of a disputed custody claim arising over a surrogate parenting arrangement or the validity of a surrogacy agreement. In sharp contrast, the laws in several U. S. states (and in Russian Federation) allow a surrogate mother to keep the child after its birth, regardless of the agreements between the intended parents and surrogate mother.

Applicable legislation. In general, applicable Ukrainian legislation lacks almost all prohibitions that are commonly found in other European countries, and offers the following advantages:

a) no limits on surrogacy related payments;

b) no additional legal procedures to obtain court order;

c) no adoption of your own child is required;

d) Ukrainian law allows to issue birth certificate to intended parents' names regardless of their genetic links to the child;

e) donor or a surrogate mother has no parental rights over the child, who is legally the child of the prospective parents from the moment of conception.

Agreements. Various agreements have to be signed between the parties, including contracts with (a) the medical institution responsible

for insemination and further medical surveillance, (b) the surrogate mother and (c) surrogacy agency (if any).

Gestational surrogacy agreement is an indispensable tool. It is also one of the most difficult agreements to negotiate and draft. Unfortunately, Ukrainian legislation does not provide any useful guidance, leaving the parties to their own devices in addressing the key issues. As a result, surrogacy agreements are usually "self-contained," highly complicated documents, reflecting many contingencies. These agreements are enforceable legal documents that will regulate the relations between surrogate mother and the intended (genetic) couple.

The surrogacy agreement must be in writing and signed before a notary prior to the embryo transfer. At a bare minimum, the following issues should be addressed: surrogate mother's health status; conditions which surrogate mother should observe; medical institution where the procedure will be performed; surrogate mother's remuneration, additional expenses, timing of payment(s); expenses connected with impregnation, pregnancy, act of delivery and registration of child; procedure of child transfer and registration; any force majeure provisions, including the delivery of handicapped child, delivery of more than one child, delivery of dead child, delivery complications resulting in surrogate mother's future infertility; confidentiality provisions and non-disclosure of information to the child or any third party, etc.

Since the Ukrainian Family Code presumes that genetic parents of the child born by a surrogacy will be a married couple, a Ukrainian notary will need to see a marriage certificate of the genetic parents, notarized and apostilled (in the USA at your home state department), translated and translation must be notarized.

Birth Certificate. Pursuant to the Ukrainian Rules for Statistic Registration, dated 18.10.2000, foreigner citizens may apply for a birth registration to the Ukrainian Vital Statistics Office. They have to submit a medical certificate that proves their genetic relationship to a child and the surrogate's written consent to record their names on the birth certificate of the child she delivered. The names of the intended (genetic) parents are written in the birth certificate upon the child's

birth. There is no need to get any special permits from any committee, court or other institution. No adoption procedure is required.

In conclusion, today's options for family formation extend beyond adoption. Advances in medical science offer intended parents a number of new pathways to parenthood. Some of these paths, such as sperm donation and traditional surrogacy, have long been in existence. Other procedures, such as egg donation, embryo transfer, and gestational surrogacy, are more recent developments in the field.

Questions for Self-checking

1. What are the main slogans of Pro-life and Pro-choice movements?
2. List the types of euthanasia.
3. In what countries the technology of surrogacy is illegal?
4. Criteria for allocation of donor organs and (or) tissues.
5. Presumed consent and dissent in transplantology.
6. Harm effect on women's health after and during abortion.

Topic 3. Bioethical aspects of experiment and clinical research. Bioethical committees: models, rights and obligations

Main lecture questions:

3.1 Eugenics: legal and bioethical issues

3.2 Organization of a scientific experiment in compliance with the basic principles of bioethics

3.3 Bioethical committees: models, rights and obligations

3.4 Clinical trials and evidence-based medicine

3.1 Eugenics: legal and bioethical issues

Eugenic considerations are not specific to behavioral genetics, though they are certainly germane. Whether and how behavioral genetics findings may be used to achieve eugenic goals is the subject of ongoing discussion and debate (e. g., Nuffield Council on Bioethics, 2002). The eugenics movement was founded by Sir Francis Galton in England in the 1860s. Eugenic means ‘‘well-born’’. Inspired by the success of plant and animal breeders, Galton wondered whether the human race might be similarly improved through a program of eugenics: we could, he thought, decrease the number of ‘‘undesirable’’ humans and increase the number of ‘‘desirable’’ ones (Galton, 1869).

Eugenics is usually divided into positive and negative varieties.

Negative eugenics involves discouraging or preventing those deemed unfit from reproducing. Involuntary sterilization is an instance of negative eugenics.

Positive eugenics is the encouragement of those deemed fit to reproduce in abundance, and to give birth only to the most perfect offspring. Though there was considerable social and scientific support for eugenics in the late nineteenth and early twentieth centuries, the technologies for achieving positive eugenics were not yet available. It is only in the past few decades that some of these technologies (such as prenatal and preimplantation diagnostic technologies) have been developed.

Combined with findings in behavioral genetics, and especially with creeping medicalization, we may witness increasing social pressure to improve humankind by eugenic means. Indeed, some have

argued (controversially) that it is morally imperative to use genetic selection technologies in support of eugenic enhancement.

Eugenics (from the Greek "noble", "the good kind") was created by *Francis Galton*, and rising to the Platon's "State" doctrine of the conditions under which the offspring is born, good for your physical and spiritual attributes, and prevented the birth of a failed generation.

For the first time this term has sounded in the book of the English biologist F. Galton "Heredity talent, its laws and consequences", published in 1869. F. Galton proposed the theory of the origin of hereditary tendencies, abilities and talents.

The author argued that the conscience, dignity and other manifestations of human higher mental abilities are biologically predetermined.

The purpose of this was to improve the teaching of "human nature" in the early stages by preventing possible deterioration of his hereditary qualities in the future through the creation and development of methods to facilitate the improvement of human qualities, such as the availability of health, mental ability, talent.

The program of the physical destruction of the mentally ill during the Third Reich in Germany included a series of sequential steps:

1) sterilization of people sicked on schizophrenia, cyclothymia, hereditary epilepsy, hereditary blindness and deafness, alcoholism, mental retardation;

2) destruction of children with physical and mental disabilities;

3) action of "T4" had gradually completed physical destruction of adult psychiatric patients by 1945.

Dachau was the first concentration camp of Nazi Germany. Created in 1933, immediately after Hitler came to power, to eliminate dissidents. Later, there were carried out medical experiments "in order to preserve the purity of Aryan blood".

By the beginning of the war Dachau camp was a perfectly well-adjusted factory killings, torture and experiments on humans with 125 offices.

During the existence of the camp to 250 thousand people passed through it from 24 countries, 70 thousand of which were brutally

tortured and killed, 140 thousand survivors of the "experiments" were transferred to other concentration camps in Germany and only 20 thousand survived until liberation.

The Nuremberg Code. The Nuremberg Code was developed during the Nuremberg trials, which is the first international document containing a list of ethical and legal principles of studies on people.

These documents were the main arguments of the prosecution at the trial in Nuremberg of the German doctors, guards and the camp commander.

The Nuremberg Code was prepared by participating in the process of US experts – physicians – Leo Alexander, Andrew Ivy, and has become an integral part of the decision of a court.

During the Nuremberg trials of Nazi war criminals, scientists and doctors announced the evidence of experiments conducted on concentration camp prisoners. Particularly cruel, inhuman nature of the experiments was the fact that they actually planned the death of subjects.

Helsinki–Tokyo Declaration of 1964–1975. It was adopted by the 18th World Medical Assembly in Helsinki (Finland) in 1964 and revised by the 29th World Medical Assembly in Tokyo (Japan) in 1975.

International Code of Medical Ethics. Adopted by the third General Assembly of the World Medical Association, London, UK, in October 1949, supplemented by the 22nd World Medical Assembly, Sydney, Australia, in August 1968 and the 35th World Medical Assembly, Venice, Italy, in October 1983.

Declaration on the Protection of Patients' Rights in Europe 1994. Source: Regional Office for Europe of the World Health Organization with the participation of the Legislation Division of the Amsterdam University of Health, 1994. May 6, 1994.

Council of Europe Convention of 1991. Adopted by the Council of Europe Convention is intended to serve as a guide for the protection of human rights and dignity in the field of biomedical science and practice.

The Convention on the protection of human rights and dignity in relation to the Application of Biology and Medicine of the United Nations (Convention on Human Rights and Biomedicine).

3.2 Organization of a scientific experiment in compliance with the basic principles of bioethics

Basic ethical principles of biomedical experiments on animals are formulated by the International Council of Medical Learned Societies (CIOMS) in the Code of Ethics (1985), includes a section "International recommendations for biomedical research using animals" and the Declaration of Helsinki of the World Medical Association (2000). In these documents, the humane treatment of experimental animals proclaimed moral obligation of scientists. It is recognized that the use of animals for scientific purposes is not desirable and should be possible to apply methods that do not require the use of animals, but at the current level of knowledge of the use of animals is inevitable.

The basic ethical principles: do no harm, and scientific validity of the study. This means that the experimenter should strive as much as possible not to cause animals pain and inconvenience, to be responsible for their situation and living conditions, and design an experiment to prove its necessity, seeking alternative ways to obtain data without involving live animals.

The criteria of need to use laboratory animals for scientific and educational purposes, and in this case are:

– perform basic scientific research that requires experimental verification;

– a pilot phase of preclinical testing, designed to produce results, not attainable by other means (developing new or improving existing treatments, the development of technology and the acquisition of knowledge for the development of new effective treatment, diagnosis or determine the etiology and pathogenesis of the disease);

– training the technique of urgent surgical interventions, mastering the skills and abilities necessary for further work in the clinic, the acquisition of which cannot be achieved by other means.

At the international level the legal basis for the legislative regulation of animal experiments is the *European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes* (number 123, 1986), which includes the main provisions of the Code of Ethics CIOMS. EU Council Directive "On the approximation of laws, regulations and administrative provisions of the Member States for animal protection issues used for Experimental and other Scientific Purposes" identified strategic ethical requirements in this regard:

a) the prohibition of using animal experiments if there is another (alternative) scientific method to obtain results;

b) a requirement to reduce the number of animals used in experiments and improvement of experimental techniques to minimize the suffering of experimental animals;

c) a requirement competence (appropriate education and skills) of individuals who may be allowed to work with animals;

d) monitoring the implementation of laws by state agencies and/or ethics committees of institutions;

e) periodic reporting, the availability of information on the use of experimental animals, and the measures taken for the protection of animals used for experimental purposes for the public;

f) the development of the international system of special education for those who work with experimental animals (the development of methods of anesthesia and surgical techniques, alternatives to animal experiments, familiarity with the laws and regulations governing the experiments, and others).

Since the late 60-ies of the last century the idea of an alternative bioassay based on the *3 R* was launched and has been steadily progressing in practice (Russell & Burch): *replace* – replace higher animals in bioassay invertebrates, cellular and molecular biological tests, *reduce* – reduce the number of higher animals in experiments due to better statistical processing of the material, and *refine* – improve the conditions of work with the animals themselves, give the best anesthesia to provide quality conditions of detention and sampling of biological material.

If the execution of the first two points at times is difficult (lack of appropriate material and technical base, software, used methods and so forth), the improvement of the conditions of work with laboratory animals should be made by the experimenter forces. It is necessary to ensure the proper use of animals, including the deletion or minimization of discomfort, stress and pain when consistent with sound scientific work practice.

The first step is the correct, rational design of experiments in which the following steps should be considered:

a) selection of animal species;

b) selection of the number of animals and the formation of working groups;

c) conducting an experiment;

d) removing animals from the experience.

Regarding the choice of animal species, the importance of this stage is determined by the need for further extrapolation – the transfer of the data on the person. To date, the whole stage is completed screening of species most suitable for carrying out specific studies. Thus, it was found that a mouse, a guinea pig, traditionally used to study the effects of allergenic chemicals etc., are more susceptible to microorganisms and their metabolic products.

According to the requirements of Good Laboratory Practice (GLP) the study of 2–3 animal species is still recommended when toxicological evaluation of new chemicals, pharmaceuticals, taking into account that the calculated data may not always be verified experimentally. This can be due to polymorphism of metabolism, e. g., xenobiotics, age and gender-related features. So, there is speculation that the list of possible causes of "thalidomide catastrophe" one of the places takes non-compliance with the criterion of the adequacy of the choice of the type of experimental animal for the study of teratogenic effects of this drug.

Select the number of animals. The unreasonably high number of animals is not uncommon in the planning of scientific work. Thus, the standard, the optimal group is 7–10 animals, but in some cases, their number can be reduced without compromising the reliability of the results. This, for example, concerns the assessment of morphological

changes in dynamics. Using linear animal experiment must be closer to international standards.

Distribution of animals in groups (depending on the age, sex, physiological properties) is also important, determination of the amount and test groups, control and reference groups. It is possible to reduce the number of experimental animals at this stage through the use of laboratory control, of a control group data for several experiments conducted in parallel.

The next stage is directly carrying out an experiment. An important role is played by the experimental laboratory equipment, in particular, equipment and tools of the operation unit. For example, the use of a CSRL BelMAPO operating table, specially designed for surgical operations and manipulations on the animals can adjust its size (angle of panels tilt to 40°) depending on the size and mass of the operated animals and required position for the operation (e. g., operating in X-rays office), to lift the distal or proximal part of the table, taking into account peculiarities of operations and manipulations depending on the diversity of interventions (in the lower or upper extremities, chest or abdominal cavities, craniotomy, etc.). This provides maximum flexibility for the location of the operating personnel, and the optimal surgical approach, which, in turn, reduces the duration of surgery, reduces injuries and accelerates the subsequent resuscitation.

During the manipulation, not requiring analgesia or anesthesia, you should avoid the use of substances and preparations with severe irritating properties.

All procedures on animals which may cause them pain or any other kind of painful state should be carried out with sufficient anesthesia (local or general anesthesia). However, taking into account that each drug substance causes narcotic effect and a number of functional changes in various physiological systems, and these changes are not the same type of character. In the formulation of experience it is necessary to take into account the peculiarities of each drug and to choose the most suitable. In determining the dosage of anesthesia, it is necessary to take into account the high sensitivity of a

number of animal species (birds, some mammals) to these drugs. Even a small overdose for many of them can be lethal.

When you use anesthesia it is prohibited to use funds, preventing control of the anesthesia level: tying the muzzle etc.

Fixation of the animal should only be performed after anesthesia will work. Animals should be tied so as not to cause them pain or damage, do not disturb the normal circulation, as well as the right not to change the position of the muscles or body parts.

The final stage of the experiment is removing the animal from the experience (euthanasia) and sampling of biological material. Euthanasia is a quick and painless killing. Dogs, cats and rabbits should be subjected to euthanasia only in a state of anesthesia (anesthesia overdose: a single dose multiplied by 3). For small animals an overdose of anesthesia, permissible quick decapitation are optimal. Inhaled anesthetics are desirable (halothane, chloroform). Studies by V. V. Rudenko have shown ether use in breeding animals from the experiment completely impractical because it distorts the results of the experiment, at least on neural tissue. It is unacceptable to use force techniques, if the animal is afraid and resists.

The following methods of killing are prohibited:

• using muscle relaxants, for pet stops breathing, but feels pain and dying, while maintaining consciousness;

• using electric current, as it may take some time for cardiac and central nervous system shutdown, during which the animal feels a sharp pain, vocal and motor reactions are absent because of the growing paralysis of the muscles; and small animals suffer more because they are more resistant to the current;

• using different kinds of poisons;

• via painful injections – intravenous, to the heart, pleura;

• using an air embolism.

A relationship (ethical, responsible, thoughtful) of the experimenter influences not only the life of animals on which experiments are carried out, but also the health and lives of the people for which they are held.

Experimentally-biological clinic (vivarium) is the scientific support unit BelMAPO created for keeping and breeding laboratory animals used in biomedical research.

Conducting biomedical research on laboratory animals is currently impossible without establishing parity desire to reach by the experimenter during the experience as much as possible the amount and accuracy of information and respect for the fundamental principles of bioethics.

3.3 Bioethical committees: models, rights and obligations

Ethical (bioethical) committees are a mechanism for ethical control over the conduct of biomedical research on humans.

The provisions of the Nuremberg Code designed during the International Military Tribunal are developed and detailed in various international and national documents and formed the basis for the work on research ethics committees.

Helsinki–Tokyo Declaration (World Medical Association – WMA, 1975) – the term "special committee" was firstly recorded in international practice (1964–1975). "The program and the execution of each experimental studies in humans should be clearly formulated in an experimental protocol which should be submitted to a specially appointed independent committee for consideration the remarks and proposals" (section 1.2 of the Helsinki–Tokyo Declaration).

The world's ethics committees operate on two levels:

- national;
- regional (local).

The main practical work on the ethical control of medical science and practice is generally carried out at the regional level.

There are following models (type) of ethics committees according to its functional purpose:

- the "American" (North American);
- the "European" model.

The "American" model is characterized by empowering ethics committees "prohibitive" privileges.

The "European" model is characterized by empowering ethics committees "advisory and consultative" authority.

In the early 70's, WMA legally documented requirements for the composition of the Ethics Committee.

The composition of the Ethics Committee should consist of at least 5 people, including a lawyer and a representative of the so-called public, which should ensure the assessment protocol of the proposed research, including from the point of view of its social importance. The remaining members of the committee should not only be the representatives of the institutions, on the basis of which it is supposed to carry out research, and should not be representatives of the same profession.

According to international standards (the Helsinki-Tokyo Declaration, and others) each research protocol must pass pre ethical review and receive approval of the relevant ethics committee.

The purpose of this examination is to protect the rights, safety, well-being and dignity of the people involved in medical-biological research and experiments as a test.

The International Bioethics Committee was established on the initiative of UNESCO in 1997.

The use of medical and biological experiments on humans may be subject to the following requirements:

1) socially useful purpose;
2) the scientific validity;
3) the advantages of the possible success of the risk of causing serious consequences to the health or life;
4) the application of the publicity of the experiment;
5) the full awareness;
6) the voluntary consent of the person subject of the experiment, with respect to their application requirements;
7) medical confidentiality, where appropriate;
8) the prohibition of experiments on the legally defined categories of persons.

3.4 Clinical trials and evidence-based medicine

Clinical trials are scientific evaluations of medical interventions for the treatment of somatic or psychological conditions that provide an analysis of the quality, safety, and efficacy of particular products,

or a method of evaluating two products for their comparative value. While clinical trials are most often used to test therapeutic pharmaceutical products, they can also be utilized to evaluate medical devices or surgical procedures, plus other preventive, screening, detection, and non-pharmacological therapeutic products/methods.

Clinical trials influence clinical practice by providing vital information to clinicians and patients to use in assessing appropriate treatment options. Clinical trials allow for the generation of sound empirical evidence that individuals can use to address important questions concerning the benefits and harms of particular therapies in a scientifically rigorous and ethical way.

At the planning stage of a clinical trial, investigators produce a research protocol that specifies the procedures and methods to be performed throughout the course of the trial. An appropriately constituted research ethics committee – be it an institutional research ethics board or a multicenter research ethics board – must approve this protocol for scientific thoroughness and ethical appropriateness. This may include, amongst other considerations, ensuring that the experimental design is sound, the number of research subjects will accurately represent an adequate statistical sample, there is a suitable informed consent process, if there is compensation being provided it is not unduly coercive, and that the proposed research is in accordance with current scientific practices and ethical/legal regulations.

Clinical trials can be randomized (RCT) and nonrandomized. An RCT comprises two (or possibly more) experimental or treatment groups/arms in which trial subjects are randomly assigned into different groups to ensure internal validity. If there are two groups, one group receives the product being studied and the other group receives the standard therapy/product, or a placebo. Where possible, the highest standards for RCTs include blinding, where the trial subjects (single-blind trial) or the trial subjects and investigators (double-blind trial) do not know which product is being tested.

Non-randomized trials are sometimes conducted where randomization is impossible for ethical or pragmatic reasons. They face greater problems of bias, although these can sometimes be limited by careful design. When new therapies are tested in humans, especially

in the case of pharmaceutical therapies, RCTs generally comprise four progressive phases.

The different types of clinical trials are as follows (with phase III trials usually being RCTs).

Phase I. In this phase, products are tested on a small number of subjects to collect data on considerations such as toxicity and best method of administration. These subjects may be healthy volunteers or patients with specific conditions, depending on the type and nature of the product. Testing in this stage seeks to collect data on the pharmacokinetic action of products in humans, possible risks or side effects associated with products at different dosages, amongst other consideration. The number of subjects participating in this phase is usually under 100. If sufficient and appropriate data are collected in this preliminary phase, it is used to design phase II studies.

Phase II. In this phase, products continue to be tested on a larger number of subjects to collect further data on pharmacological and pharmacokinetic activity, particularly in patients with the condition the product is proposed to treat. It is also at this stage that the new product is measured against the standard treatment or placebo for its comparative efficacy. The number of subjects participating in this phase is usually no more than several hundred. If sufficient and appropriate data are collected in this secondary phase, it is used to design phase III studies.

Phase III. In this phase, the product is tested on an even larger number of subjects in a continued effort to evaluate the product's safety and efficacy, especially in relation to standard treatments or placebos. At this stage, the product is generally dispensed as it would when it is to be marketed, and it is evaluated for its overall risk–benefit relationship and clinical labeling profile. The number of subjects participating in this phase is usually several hundred to several thousand.

Phase IV. In this phase, which occurs only after the product has been approved and licensed for use, the product is evaluated for potential long-term side effects associated with the drug. This postmarketing surveillance phase could also include studies concerning how different dosages, schedules, or length of

administration of the product affect patients, or how different patient populations react to the product.

In addition to the important exchange of information between study investigators, sponsors, and institutional/regulatory bodies, it is essential that the dissemination of results from clinical trials – positive, negative, and inconclusive results – occurs through peer-reviewed conferences and peer-reviewed journals; even if the results are unpublished, it is important that they are registered in a clinical trials registry. This ensures that clinicians and patients have access to the best information possible to make responsible decisions about what medical interventions are worthwhile undertaking.

The ethical importance of clinical trials is sometimes underestimated. Yet the need to evaluate treatments for their safety and efficacy, so as to minimize harm to patients, reduce clinical uncertainty, and improve the efficiency of resource allocation, is great, as has been recognized since Archie Cochrane's (1972) lectures on Effectiveness and Efficiency and the rise of the **evidence-based medicine** movement. Much more attention has been paid to the ethics of the conduct of clinical trials. The standard principles of research ethics apply to clinical trials, such that the avoidance of coercion and undue inducement, the properly informed consent of the patient, the proportionality of risk and benefit, and the scientific and clinical competence of the investigators all need to be assured. In recent years, attention has focused on the need to warrant randomization in clinical trials. The principal theory of the ethics of randomization is the "equipoise" theory. On this theory, clinicians discharge their responsibilities to do their best for their patients if, faced with genuine uncertainty as to which one of the available treatments is most effective (or safest) in treatment of a condition, they allocate the patient treatment by randomization, thereby giving the patient an equal chance of receiving the treatment which is actually most effective.

At issue is the question of whether the uncertainty is genuine, and whether the patient understands this. Some patients can experience the "therapeutic misconception", according to which they believe that the treatment they are receiving must be the treatment that is best for them, when this is actually not certain and the treatment is

in a broader or narrower sense ‘‘experimental’’. Current best practice is that uncertainty should be underwritten by the conduct of an appropriately rigorous systematic review of the existing clinical evidence before a trial is initiated; and a stronger claim is sometimes advanced, that where uncertainty exists a trial ought to be initiated.

In practice, not all clinical trials exist to resolve clinical uncertainty, since many trials are run in order to establish the safety and licensure credentials of a new treatment, rather than to assess the merits of a new treatment in the light of the alternatives.

Often there can be moral conflict in clinical trials between an investigator’s scientific duty and protective duty – with the predominant view being that, when in conflict, the protective duty must override scientific duty. Merritt (2005) has recently argued that, in such conflicts, we need not choose one duty over the other; instead, in hard cases, investigators should proceed by taking into consideration the interests that research subjects have in achieving their personal goals for participation in research.

Evidence-based medicine (*EBM)* is to use in everyday medical practice (in the diagnosis, treatment and prevention), medical technology and medications effectiveness of that has been proven in pharmaco-epidemiological studies using mathematical estimates of the probability of success and risk.

The main principle of EBM is every clinical decision should be based on scientific facts, reported a statistically representative at a large group of patients.

The main method of EBM (Gold standard) is a randomized, controlled study in which patients are divided into groups randomly.

There are following main pharmaco-epidemiological concepts to obtain evidence of the effectiveness of medical technologies:

- the actual (final) clinical outcome;
- mediated (indirect) the criterion of effectiveness;
- the absolute risk;
- the relative risk.

Questions for Self-checking

1. What does the term “eugenics” mean?
2. What powers do the ethical (bioethical) committees have?
3. What qualities must the scientist-experimenter have?
4. What is the main task of ethics committees?
5. What work belongs to Francis Galton?
6. Which international document contains ethical and legal principles for research on humans?
7. What is Evidence-based medicine?

Topic 4. Modern biotechnology and biosafety software problems. Genetically modified organisms

Main lecture questions:

4.1 Biological hazard and levels of biosafety

4.2 Basics of biotechnology

4.3 Ethical issues of genetic engineering technologies

4.4 Genetically modified organisms

4.5 Genetic screening in pregnancy and abortion. Stem Cell research

4.1 Biological hazard and levels of biosafety

Biosecurity is a system of evidence-based measures to prevent or reduce to a safe level the potential adverse effects of genetic engineering and genetically engineered (transgenic) organisms on human health and the environment.

The most important agreement regulating inter-state relations in this sphere is the *Cartagena Protocol on Biosafety* (2000), the *Convention on Biological Diversity* (1992).

Justification of biosafety mechanisms as a system of measures "to ensure the secure creation, use and transboundary movement of living modified organisms resulting from biotechnology", occupy a leading position in modern bioethics.

The term *"biological hazard"* means "an infectious agent (or part of it), representing a potential danger to human health, animal and/or plant through direct effects: infection or indirect influence: through the destruction of the environment".

For different groups/categories of laboratory infections elaborated practical guidelines that describe the appropriate equipment for the safe storage of biological material, the necessary equipment and activities to be performed by laboratory personnel. These guidelines are called biosafety levels (BSL). There are four levels, each of which consists of the primary and secondary barriers and microbiological procedures features.

The first level corresponds to the minimum risk of infection; work with microorganisms of pathogenicity class 4 requires compliance with the maximum precautions.

Biosafety Level 1. Rules of work, in accordance with safety equipment and laboratory premises, are suitable for use with known strains of microorganisms with which human cases of the disease are not registered. The laboratory does not have to be isolated from the premises of the building. Work may be performed on a conventional lab bench to standard microbiological procedures. Special protective equipment required and/or is not used. Laboratory personnel passes the usual safety training and is under the supervision of the chief laboratory with experience in a standard microbiology laboratory. Biological safety cabinet when working with these strains of microorganisms are not required.

Biosafety Level 2. Rules of work, in accordance with safety equipment and laboratory premises, are suitable for a wide range of known microorganisms belonging to the moderate-risk group, causing human disease of moderate severity.

The main differences from the Biosafety Level 1 are:

a) laboratory personnel receive specific training in handling pathogenic microorganisms under the guidance of experienced professionals;

b) the access to the laboratory is limited during the operation;

c) careful handling of sharps is recommended;

d) special precautions for handling are required, in which aerosols and/or spray can be formed. We recommend the use of physical barriers to protect. It is highly recommended to work in a biological safety cabinet class I and class II.

Biosafety Level 3. Rules of work are in accordance with safety equipment and laboratory space suitable for working with local and exotic microorganisms transmitted by airborne droplets and cause severe illness or even death. Particular attention should be paid to the protection of personnel (primary and secondary barriers) as well as the protection of society and the environment. Essential requirement: works in the biological safety cabinet class I and class II.

Biosafety Level 4. Rules of work are in accordance with safety equipment and laboratory space fit for work with dangerous and exotic strains of microorganisms that represent a high risk to human health and life. Diseases are transmitted by airborne droplets or unknown ways and do not respond to treatment; drugs and vaccines are not available. Laboratory personnel undergo special training and a thorough safety work with dangerous microorganisms and is under the supervision of a specialist who has experience of such work. Entrance to the laboratory is strictly limited. The laboratory is located in a separate building or in a completely isolated part of the building. Special rules of work in the laboratory. The presence of a biological safety cabinet class III is strictly necessary.

Practical advice on biosafety.

1. The laboratory should always take precautions when dealing with blood and body fluids, as well as the use/storage of sharp objects, to conduct treatment arms (universal precautions).

2. Do not eat, drink or smoke in the laboratory. Food cannot be stored in cold rooms used for the storage of clinical material.

3. Do not spend mouth pipetting – use the appropriate mechanical devices.

4. Disinfect countertops daily, if necessary (in case of accidental contact with the biological material).

5. Use latex gloves of a suitable size.

6. It is necessary to use face shields or masks and eye protection in situations where there is a high probability of accidental exposure to blood and body fluids.

Table 4.1 – Characteristics of biological safety levels

Level	Microorganisms description	Examples of microorganisms	Safety Rules	Necessary equipment (primary barrier)	Optional equipment (secondary barrier)
1	2	3	4	5	6
1	Do not cause the development of infections in healthy adults	Bacillus subtilis, Naegleria gruberi, Infectious canine	Standard rules of work in the lab	Does not require	Sink
2	Associated with human diseases. Transmission risk: damage to the skin, ingestion, mucous membranes	Measles virus, Salmonellae, Toxoplasma spp	Level 1 and: • access limitation; • signs of biological hazards; • strict precautions; • waste management and medical supervision.	Biological safety cabinet class 1 and 2. Personal protection: gown, gloves, mask (if necessary) Level 1 and the presence of the autoclave	Level 1 and the presence of the autoclave

Continuation of Table 4.1

1	2	3	4	5	6
3	Dangerous bacteria, usually transmitted by aerogenic route, can lead to diseases with a fatal outcome	M.Tuberculosis, St. louis encephalitis virus, Coxiella Burnetti	Level 2 and: • access limitation; • decontamination of waste and laboratory clothing; • medical monitoring employees	Biological safety cabinet class 1 and 2, and physical barriers for all open manipulations. Personal protection: gown, gloves, mask (if necessary)	Level 2 and: • separation of the laboratory from the common areas; • system self-closing double doors; • lack of the recirculation exhaust air; • creation of a low-pressure laboratory
4	The microorganisms that cause life-threatening or intractable infection treatment, transmitted mainly by aerogenic route (e. g., viruses of hemorrhagic fevers)	Ebolla Zaire, Sin Nombre virus, Rift Valley Fever	Level 3 and: • changing of clothes before entering the lab; • shower after coming out of the lab; • full decontamination clothes after leaving the lab	Biological safety cabinet class 3 or biological safety cabinet class 1 or 2 in combination with special coveralls for staff (completely closed body, air flow, high blood pressure)	Level 3 and: • the location of the lab in a separate building (or strictly isolated); • the separate feeder/vacuum release system of decontamination; • adherence to additional requirements for microbiological and biomedical laboratories

4.2 Basics of biotechnology

Biotechnology involves the use of living organisms in industrial processes – particularly in agriculture, food processing, and medicine. Biotechnology has been around since the dawn of time, ever since humans began manipulating the natural environment to improve their food supply, housing, and health. Biotechnology is not limited to humankind. Beavers cut up trees to build homes. Elephants deliberately drink fermented fruit to get an alcohol buzz. People have been making wine, beer, cheese, and bread for centuries.

The reason of biotechnology as modern is because of recent advances in molecular biology and genetic engineering. Huge strides have been made in our understanding of microorganisms, plants, livestock, as well as the human body and the natural environment. This has caused an explosion in the number and variety of biotechnology products.

"Red" biotechnology is the production of pharmaceuticals for the diagnosis and treatment of various human diseases and correction of the genetic code.

"White" biotechnology is the production of enzymes and biomaterials for the food industry.

"Green" biotechnology is the development and introduction to the culture of genetically modified plants, the creation of new animal breeds.

Genetically modified plants have genes inserted to protect them from insects, thus increasing the crop yield while decreasing the amount of insecticides used. Medicines are becoming more specific and compatible with our physiology. For example, insulin for diabetics is now genuine human insulin, although produced by genetically modified bacteria. Almost everyone has been affected by the recent advances in genetics and biochemistry.

Each organism, even the lowly gene creatures, is based on DNA. DNA and RNA have unique structures that ensure their survival and existence in all facets of life. Each structure has a backbone of alternating phosphate molecules with sugar residues. In DNA, the sugar, deoxyribose, is missing a hydroxyl group on the 2′carbon. The bases, which attach at the 1′carbon, form pairs so that adenine joins

with thymine and guanine joins with cytosine. These pairs are held together with hydrogen bonds that induce the two backbones to twist into a double-stranded helix. In RNA, the sugar, ribose, has one extra hydroxyl group, and the base thymine is replaced with uracil.

Many different organisms are used in biotechnology research, and they have a particular trait that is useful to study new genes.

Gramnegative bacteria (fig. 4.1) have three structural layers surrounding the cytoplasm. The outer membrane and cytoplasmic membrane are lipid bilayers, and the cell wall is made of peptidoglycan. Unlike eukaryotes, no membrane surrounds the chromosome, leaving the DNA readily accessible to the cytoplasm.

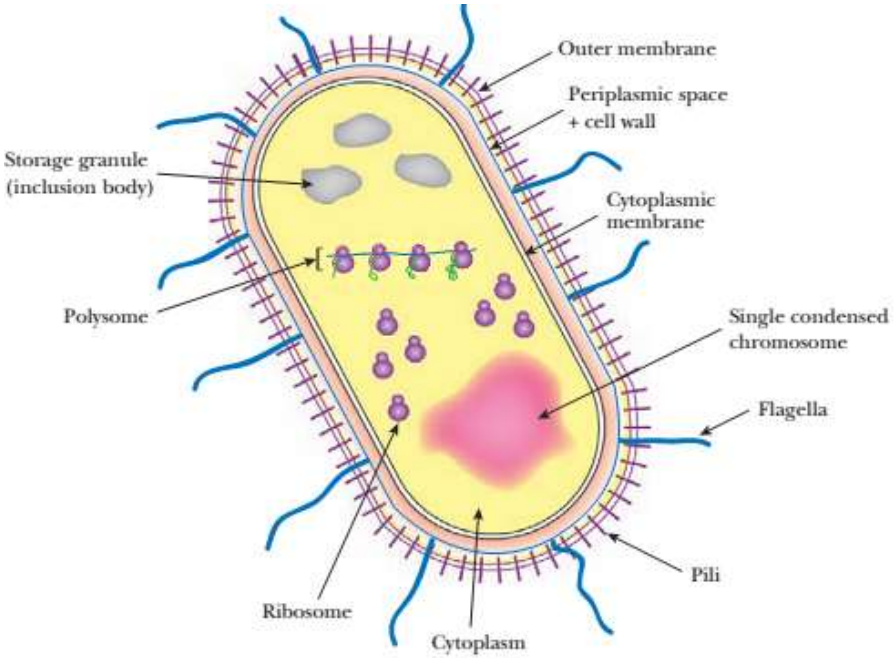


Figure 4.1 – Subcellular Structure of Escherichia coli

Bacteria are genetic clones that are easily grown and stored for long periods of time. Two key traits are their simple genomes and availability of plasmids to alter their genetic makeup. Although useful, bacteria are prokaryotes and differ greatly from humans. Therefore,

eukaryotic model organisms are also used for research. Yeasts are single-celled eukaryotes that have similar traits to human cells, such as multiple chromosomes, a nucleus, and various organelles. In addition, yeasts also have plasmids in which extra genes can be added to study in a model organism. Finally, the chapter outlines the key traits of multicellular organisms from barely visible roundworms such as *C. elegans* to mice, cultured human, animal, and insect cells, and the model plant organism, *Arabidopsis*.

Besides real organisms, research in biotechnology relies on gene creatures such as viruses, transposons, and plasmids. These genetic vehicles are critical to manipulating the genome of the model organisms. In fact, viruses may be the key to accomplishing gene therapy in humans also.

Viruses are used as vehicles to inject foreign DNA into a host cell. Transposons are also used to deliver new genes into the host DNA. Plasmids are used for the same purpose, but do not work in higher organisms and, therefore, are restricted to cultured cells, yeast, and bacteria. The use of gene creatures and model organisms is key to biotechnology research.

4.3 Ethical issues of genetic engineering technologies

Genetic engineering means that we alter an organism permanently so that the changes will be stably inherited.

Introducing genes technique into bacteria has been developed after Frederick Griffith discovered the phenomenon of bacterial transformation.

Transfer desired genes within the vector may be accomplished using several methods, such as:

– microinjection;
– electroporation;
– transport DNA liposome composition;
– microparticle bombardment (ballistic transformation method);
– use of the bacterium *Agrobacterium tumefaciens*.

For multicellular organisms this implies deliberate alteration of the DNA in the germline cells. In contrast, gene therapy (occasionally

called genetic surgery) is less permanent. The patient is cured, more or less, by altering the genes in only part of the body.

For example, cystic fibrosis patients might be partially cured by introducing the wild-type gene into the lungs. However, these changes are not inherited, and the alleles in the germline cells remain defective.

The main steps involved in replacement gene therapy are as follows:

a) identification and characterization of gene;

b) cloning of gene;

c) choice of vector;

d) method of delivery;

e) expression of gene.

Severe combined immunodeficiency (SCID) occurs when both the B cells and T cells of the immune system are defective and results in an almost totally defective immune response. Children with SCID have to be shielded from all contact with other people and are kept inside special sterile plastic bubble chambers. Without immune protection any disease, even a cold, could prove fatal. Several genetic defects are known that cause SCID. About 25 % are due to mutations in the ***Ada gene*** that encodes the enzyme ***adenosine deaminase***. This is needed for the metabolism of purine bases, and its absence prevents development of lymphocytes (white blood cells including both the B cells and T cells).

The first successful instance of human gene therapy used a retroviral vector to provide a functional copy of the Ada gene to a child with SCID. The cells affected by SCID are the lymphocytes that circulate in the blood, where they carry out immune surveillance. They are produced by division of bone marrow cells (Fig. 4.2). Gene therapy involves removing bone marrow cells from the patient and maintaining them in cell culture outside the body.

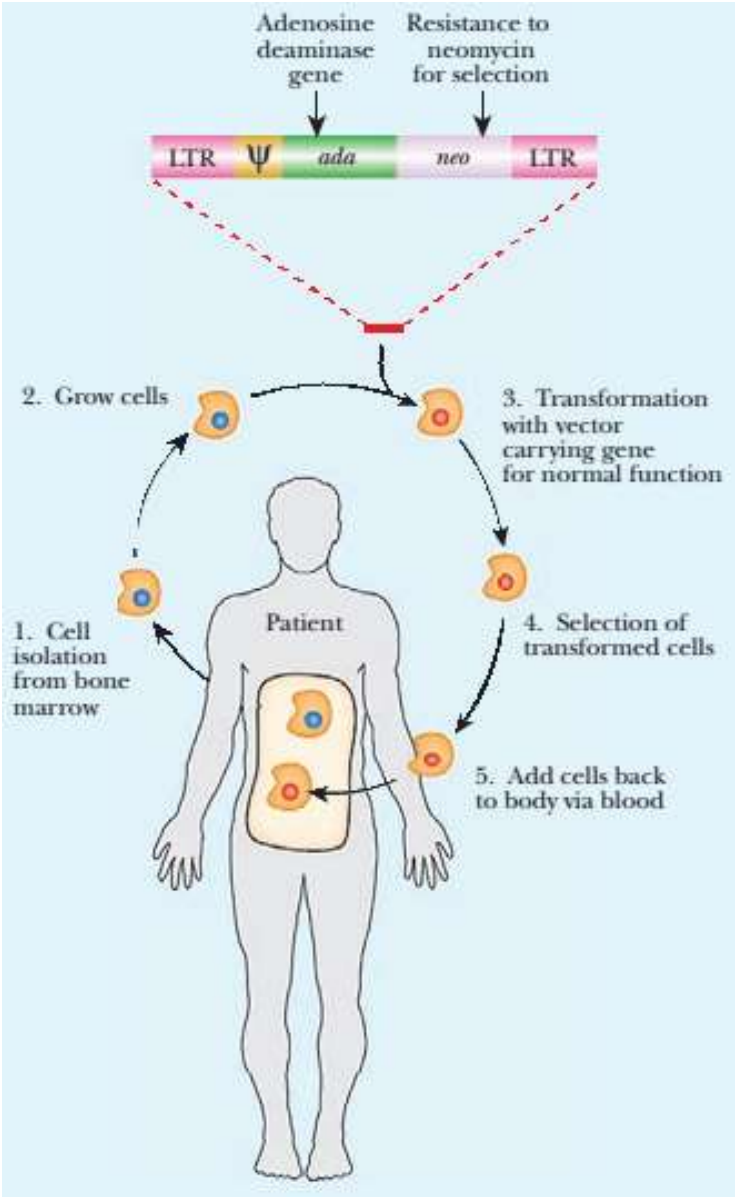


Figure 4.2 – Ex Vivo Retroviral Gene Therapy for Ada Deficiency

About 75 % of gene therapy trials have used viral vectors. A variety of alternative approaches have also been investigated, though few have been effective or widely used so far. These include:

a) use of naked nucleic acid (DNA or less often RNA). Many animal cells can be transformed directly with purified DNA. The therapeutic gene may be inserted into a plasmid and the plasmid DNA used directly. Some 10 % to 20 % of gene therapy trials have used unprotected nucleic acid;

b) particle bombardment. DNA is fired through the cell walls and membranes on metal particles. This method was originally developed to get DNA into plants. However, it has also been used to make transgenic animals and is occasionally used for humans;

c) receptor-mediated uptake. DNA is attached to a protein that is recognized by a cell surface receptor. When the protein enters the cell, the DNA is taken in with it;

d) polymer-complexed DNA. Binding to a positively charged polymer, such as polyethyleneimine, protects the negatively charged DNA. Such complexes are often taken up by cells in culture and may in principle be used for ex vivogene therapy;

e) encapsulated cells. Whole cells engineered to express and secrete a needed protein may be encapsulated in a porous polymeric coat and injected locally. Foreign cells excreting nerve growth factor have been injected into the brains of aging rats. The rats showed some improvement in cognitive ability, suggesting that this approach may be of value in treating conditions such as Alzheimer's disease;

f) liposomes are spherical vesicles composed of phospholipid. They have been used in around 10 % of gene therapy trials (see later discussion).

4.4 Genetically modified organisms

Transgenic Crop plants. There has been considerable controversy over the use of transgenic plants in agriculture.

Although the term genetically modified organism (GMO) is often used, we should remember that all domesticated plants and animals have been genetically modified by more traditional methods and consequently differ greatly from their wild ancestors. There are

three main issues to consider for transgenic crops. First is whether the food product is safe for human consumption. Second is the question of containment. Third is the question of hazard to the environment.

Containment of transgenic plants is unrealistic on an agricultural scale. In practice, seeds from different batches of corn are impossible to keep wholly separate, and mixing of GMO with natural corn has occurred. DNA of transgenic origin has been detected in wild plants. For example, wild maize (corn) in Mexico examined in 2001 contained transgenic DNA, even though planting transgenic corn plants was stopped in 1998. Worrisome possibilities include genes for herbicide resistance moving from crop plants to weeds. This would make weed control more difficult. Similarly, insecticide toxins expressed in pollen grains might harm bees, impairing the pollination of crops that depend on the bees.

Perspectives on GMO food vary greatly (Table 4.2) but seem rather predictable, based on known vested interests. Those who grow, export, and profit from GMO crops claim that they are safe and that the controversy is largely an emotional overreaction. Originally, the corporations and farmers were overall pro-GMO. However, the terminator controversy caused a rift between these two groups. Environmental and consumer groups tend to oppose GMO, as with any new technology.

Table 4.2 – Percentage of GM Crops by Region (2004 Data)

Country	**%**
USA	59
Canada	6
Argentina	20
Brazil	6
China	5
Others	4

Loss of Biodiversity. Genetic engineering followed by cloning to distribute many identical animals or plants is sometimes seen as a threat to the diversity of nature. However, humans have been replacing diverse natural habitats with artificial monoculture for millennia. Most natural habitats in the advanced nations have already been replaced with some form of artificial environment based on mass production or repetition. The real threat to biodiversity is surely the need to convert ever more of our planet into production zones to feed the ever-increasing human population. The cloning and transgenic alteration of domestic animals makes little difference to the overall situation.

Conversely, the renewed interest in genetics has led to a growing awareness that there are many wild plants and animals with interesting or useful genetic properties that could be used for a variety of as-yet-unknown purposes. This has led in turn to a realization that we should avoid destroying natural ecosystems because they may harbor tomorrow's drugs against cancer, malaria, or obesity.

One divisive aspect of the GMO controversy was the development of "terminator" technology. Crop plants were engineered so that their seeds would be sterile. The pretense was that this would prevent escape of GMO plants into the wild. The underlying motive was mere greed. Farmers would be forced to buy a new supply of seeds each year instead of planting seeds saved from the previous year's harvest. This would both increase the profits of the seed corporation and make farmers dependent on their seed suppliers. The attempted use of terminator technology to blackmail farmers caused a great deal of ill feeling.

The terminator scheme involves three transgenes:

1. A gene for a toxin that is lethal only in developing seeds. The toxin gene is otherwise inactive due to a DNA spacer flanked by *loxP* sites inserted between the promoter and the coding sequence.

2. A gene for Cre recombinase, which recognizes the *loxP* sites and recombines them so deleting the spacer sequence. This allows expression of the toxin gene.

3. A gene encoding a variant of the TetR repressor that prevents expression of the Cre recombinase gene.

Before sale, the seeds are soaked in a solution of tetracycline that binds to and inactivates the repressor. This allows the Cre recombinase to become active and remove the spacer sequence. The toxin gene is now expressed. Because the toxin does not harm the growing plant, except for the developing seeds, the crop grows normally except that the seeds are sterile.

Transgenic Animals and Animal Cloning. Humans have meddled with nature since time immemorial. Historically humans have altered animals and plants by deliberate selective breeding and hybridization. In addition, human activity has led to unconscious genetic modification of many organisms. For example, we have undoubtedly selected alterations in the mice that infest our fields and grain storage facilities and the insects that rely on human crops. The novelty of genetic engineering is not in what we are doing, but in how we do it. Today we generate transgenic organisms by direct manipulation of their genetic material.

Even if you devote a whole field to growing a crop plant that is natural, you are eliminating the natural inhabitants of that patch of land. Moreover, you will select for life forms – both weeds and insect pests – that adapt to croplands. The European corn borer is a huge threat to the corn crop, but if we did not grow so much corn, these insects would be rare. Whether we want to or not, whether we are aware of it or not, we are imposing genetic selection on many other organisms, whatever we do.

Genetic manipulations could create future organisms that are truly bizarre by today's standards. By manipulating the homeobox genes, which control body plans and segmentation, maybe a "chickapede" – a chicken with multiple legs and body segments – could be created. Perhaps more grotesque would be to develop feed animals lacking most of the brain. This would avoid the suffering of domestic animals that are kept for slaughter. The controversy surrounding such future creations is yet to arise.

4.5 Genetic screening in pregnancy and abortion. Stem Cell research

Genetic screening of newborn babies has been practiced for some time. Such information is used to allow early treatment of newborn infants, the classic case being phenylketonuria (PKU). People with PKU lack the enzyme that converts phenylalanine to tyrosine, and excessive amounts of phenylalanine causes permanent brain damage.

Newborn screening allows infants with PKU to be given a diet low in phenylalanine, greatly reducing the damage. More recently it has become possible to screen developing fetuses for a variety of genetic defects long before birth. Analytical techniques are constantly advancing and an ever-increasing list of inherited defects can be monitored, at ever earlier stages of development.

However, prenatal genetic screening could also be used to decide whether to abort a fetus destined to suffer from an inherited defect. As understanding of the human genome increases, it will become possible to deduce such things as the probable future height, eye color, IQ, and beauty of the developing fetus. Most parents would like to have smart, healthy, and attractive children, and the temptation to have abortions based on these characteristics will soon become a reality.

The abortion issue is of course a peculiarly American obsession. Most European nations legalized abortion in the 1950s, and few Europeans take seriously the moralistic pronouncements on this issue that come from the other side of the Atlantic. The central question of the abortion issue is “When does human life start?” From a biological perspective, life does not start at one particular point but is a continuum. Sperm cells are alive, and so are the eggs they fertilize. Fusion of egg and sperm to create a zygote forms a new living individual with a unique genetic constitution. Rather than the beginning of life, the issue is perhaps really about consciousness. When do we actually become a conscious being? This is impossible to answer because no one yet understands consciousness, let alone has the ability to measure it.

Because society has arbitrarily decided that abortion is legal until the end of the first trimester, who should decide if an abortion is to be performed? From a genetic viewpoint, both father and mother have an equal share in the new individual – except for the mitochondrial DNA that is maternal in origin. From the viewpoint of biological resources, the mother has more invested and has traditionally been allowed to make the decision.

Thus, the father often has fewer rights over the children. Although this outlook was not deliberately based on evolutionary considerations, it does in fact coincide with Darwinian logic.

Stem Cell research. Another issue that has become entangled with the abortion controversy is stem cell research. Stem cells are the precursors to the differentiated cells that make up the body. Different types of stem cells correspond to different types of tissues. Embryonic stem cells are found in the developing embryo and retain the ability to develop into any body tissue. Embryonic stemcells can be maintained in culture and may be used to create transgenic animals by insertion of DNA.

It is hoped that engineered stem cells will eventually be used to regenerate damaged tissues or organs. One controversy concerns the source of the embryonic stem cells. In particular, should they be taken from discarded fetuses? One side claims that stem cell research will encourage abortions just to provide material. The other side claims that stopping research will deny patients medical improvements such as organ replacements. A related issue is the use of stem cells from leftover embryos in fertility clinics. Because few stem cells are needed for research, and vast numbers of aborted fetuses already exist, increased numbers of abortions seems unlikely.

In addition, no one has yet grown an actual human organ from a stem cell. Thus this controversy is based on possibilities, not realities. One suspects that if technology advances far enough to grow organs in culture, it will also allow the use of stem cells from the patient's own body and embryonic tissue will no longer be required.

Stem cell research merges into other areas of biotechnology. If scientists are not allowed to use existing aborted tissue, can they create their own embryos in vitro? How far should such embryos be allowed

to develop? Should brain tissue be used, since that is where people believe our consciousness lies?

Forensics and Crime. Obviously any technology that is used to combat crime can be abused. Forensic Molecular Biology, the use of DNA for identification in both criminal investigations and civil cases (mostly paternity suits) is now widely accepted (Fig. 4.3).

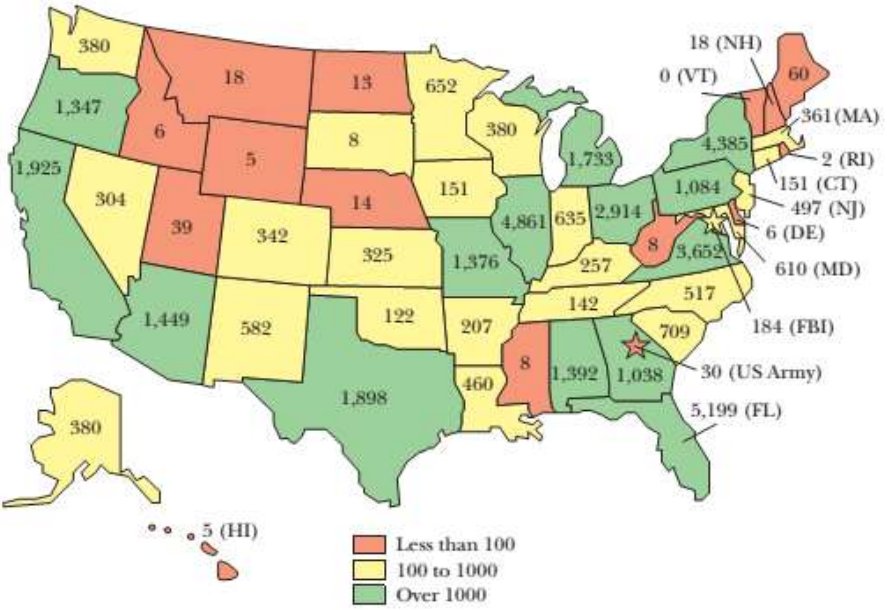


Figure 4.3 – Acceptance of DNA Evidence in Today's Culture

Early technical problems have been ironed out, and the probabilities are now so overwhelming that, when properly done, DNA analysis can give a reliable and essentially unique identification. In fact, one major result of using DNA evidence has been the release of significant numbers of suspects who were wrongly convicted based on less reliable means of identification.

The remaining ethical issues concern such matters as setting up national or international databases of criminal DNA records. Who will be included? Who will have access? At the moment, DNA sequences used in identification are located in regions of noncoding DNA. However, it may eventually be possible to deduce a person's physical

appearance and mental characteristics from DNA. If this is feasible, will DNA left at a crime scene be further analyzed to provide this information about possible suspects?

New advances in both knowledge and technical capability bring new ethical and regulatory problems. Closer inspection suggests that many new ethical issues are merely old issues in a new guise. Other issues do not involve ethics so much as familiarity. Nonetheless, some aspects of genetic engineering, such as transgenics and human cloning, do pose questions that are at least partly new.

Questions for Self-checking

1. Should people be allowed to clone their pets?
2. Is prescientific selective breeding accepable?
3. Is applying Mendelian genetics acceptable?
4. Is genetic engineering admissible as long as no foreign DNA is introduced from another species?
5. Would it be good enough to develop a chicken with, say, 10 legs for food?
6. Are European views on abortion (and related issues) more advanced or more degenerate than American attitudes?
7. Should prenatal genetic screening be allowed for inherited diseases?
8. Should defective fetuses be terminated by abortion? Who should make the decision whether a defective fetus lives or dies?
9. Should we enforce paternity tests to make sure that the true genetic parents of a child are notified of any decisions about the child's welfare?

Topic 5. Infectious diseases and problems of biosafety. Bioterrorism as a threat to biological security

Main lecture questions:

5.1 Infectious diseases: ethical and biosafety issues

5.2 History of biological weapons

5.3 Bioterrorism and germ warfare

5.4 Long-term biological problems

5.1 Infectious diseases: ethical and biosafety issues

Infections are important because they are major causes of disease, death, and disability. Paradoxically, most are curable and many are preventable. They are unique in that they can be knowingly or unintentionally transmitted from person to person. They cause serious epidemics and devastating pandemics. Finally, despite remarkable technical progress that has radically diminished the incidence of childhood infections in developed countries and entirely eliminated smallpox, new infectious diseases such as *Ebola virus infections*, *severe acute respiratory distress syndrome (SARS)* and *Avian influenza* continue to emerge, evolve, and kill significant numbers of people and frighten and threaten many more. Infectious diseases entail some unique ethical features that are often encountered by public health officials.

The fact that nearly all infectious diseases are caused by microorganisms and that many are relatively easily transmissible, diagnosable, treatable, curable, and preventable leads to the characteristic ethical problems that arise in the context of this class of diseases. Patients often bring these problems directly to physicians when they present for diagnosis, treatment, or preventive care.

Ethical problems arise from conflicts between values, principles, and interests. Infectious diseases ethics examines how features of infection shape these problems, especially the tension between honoring patients' preferences and preventing harm to others.

The transmissibility of an infection, such as *tuberculosis* or *gonorrhea*, places a physician's duty of confidentiality to the patient in conflict with a duty to society and an obligation to obey the law.

This may entail reporting the infected patient to public health authorities so that they can investigate an epidemic, alert contacts, and arrange diagnostic testing and treatment. Such mandatory reporting may be inconsistent with the patient's expectation of confidentiality. The doctor can remind the patient that he, himself, can alert his contact(s) to their exposure and reduce the shock of a public health visit.

Because diagnostic tests for infection in symptomatic and even asymptomatic individuals have value to others, the usual calculus of benefit and risk to the patient may be expanded to include those benefits. The standard practice of voluntary informed consent may be modified to accommodate strong recommendations, presumed consent, or required testing. It was common practice in the USA, for instance, to test all hospitalized patients for syphilis without their informed consent when this infection was more prevalent. Screening of refugees for the *human immunodeficiency virus* (HIV) and *hepatitis B* is currently carried out.

The generally safe, effective, brief, and relatively inexpensive treatment and cure of infectious diseases make it unusual for patients to refuse treatment and more difficult for doctors to understand and accept such refusals. If the patient's infection is likely to be transmitted to others, as tuberculosis would be, his/her refusal is even more problematic. As so many infectious diseases can be prevented, physicians have opportunities and perhaps a duty to recommend measures to prevent them.

Sometimes this could help patients to avoid a serious, difficult to treat infectious disease such as tetanus. In many cases, like *measles* or *hepatitis B*, disease prevention for the patient, such as immunization, also provides protection for the community.

Therefore, the physician may not always be able to offer the patient the usual option to refuse an intervention since some immunizations, such as polio and yellow fever, may be required for school entry or travel to another country.

Because some infectious diseases, such as *meningitis*, occur suddenly, advance rapidly, and impair cognitive function, there may be only a brief time during which patients can participate in medical

decision making. Although most patients acquiesce quickly to diagnostic tests and antibiotic treatment, refusals of either can be very disconcerting. It is important to investigate the patient's reasons for refusing a diagnostic test and correct any misunderstandings that contribute to the refusal. The person-to-person transmissibility of infectious disease in the context of a medical encounter makes this category of diseases unique and raises special ethical issues. The problem was first recognized by transmission of group *A streptococci* on doctors' hands to obstetric patients, who developed puerperal fever. Recent concerns have focused on the possible, but rare, transmission of hepatitis B and HIV between patient and doctor or dentist.

Does the doctor have an obligation to accept some level of personal risk to care for a patient with a communicable disease? Does a doctor with a transmissible infection have a duty to avoid or anticipate the risk of transmission and, if the risk is not eliminated, to disclose it to patients?

The duty to do good for the patient and provide competent medical care is not obviated by an exaggerated fear of personal risk. Doctors with no likely exposure to a patient's blood or bodily fluids have no basis for avoiding their duty to care for their patient with an infection transmitted via these fluids. Clinicians who risk such accidental exposure in the course of surgery or procedures have an understandable concern about personal risk. An appropriate way to address it is to use prevention when possible, such as personal immunization against hepatitis B, universal precautions, safe needle use, and masks and gowns when appropriate to minimize transmission of blood- and fluid-borne pathogens.

It is not appropriate to test patients for infections like HIV surreptitiously and/or decline to provide medically necessary treatment to them because of a known or suspected infection. If medical treatment is withheld for that reason and the doctor offers an alternative but untrue explanation for the refusal, it is even more ethically inappropriate.

If a doctor has likely been exposed to a transmissible pathogen, he/she has two reasons to determine if an infection has occurred. The first is their personal health, since many infectious diseases such as

HIV, hepatitis B, and syphilis can be averted or effectively treated if suspected or diagnosed at a very early stage.

The second is to prevent inadvertent transmission to a patient. If a doctor discovers that he or she has an infectious disease transmissible in the context of their practice, the doctor should comply with the policy that governs such situations in that institution. In the absence of a policy, doctors should seek advice from an infectious disease specialist, preferably the hospital's infection control officer and also determine whether any overriding public health policies apply.

5.2 History of biological weapons

Early attempts. The early use of biological weapons included the contamination of water with animal carcasses and filth. Another ancient tactic was to allow an enemy to take sanctuary in an area endemic for an infectious agent in anticipation that the enemy force would become infected, for example, allowing unimpeded access of opposing forces to areas where transmission of malaria was highly likely. One of the most notorious early biological warfare methods was the hurling of cadavers over the walls of besieged cities, primarily as a terror tactic. De Mussis provided a dramatic record of the use of *plague* victims in biological warfare. The plague, later known as the Black Death, was spreading from the Far East and reached the Crimea in 1346.

Smallpox was particularly devastating to Native Americans. The unintentional yet catastrophic introduction of smallpox to the Aztec empire during the Narváez expedition of 1510, and its subsequent spread to Peru in advance of Pizarro's invasion of the Inca empire, played a major role in the conquest of both empires.

At the conclusion of the French and Indian War in 1763, the Native Americans conducted a series of attacks against British forts along the western frontier in what is known as Pontiac's Rebellion. An outbreak of smallpox at Fort Pitt presented an opportunity to take advantage of the Native Americans' unique susceptibility to this disease.

The early era of modern microbiology and the world wars. The birth of scientific bacteriology during the 19th century provided the

scientific and technical basis for modern biological weapons programs. The Hague Conventions of 1899 and 1904 outlawed the use of "poison or poisoned arms", although the possible use of bacteriological weapons was not specifically identified or addressed. Germany started the first known scientific, state-sponsored biological weapons program during World War I.

Sixteen espionage agents reportedly undertook a covert biological campaign in the United States before the United States entered the war. The Allies had purchased US draft animals for military use, and German operatives infected these animals with *glanders* and *anthrax* while they were awaiting shipment overseas.

The Germans also conducted similar operations in Romania, Russia, Norway, Mesopotamia, and Argentina, with varying levels of success. Attempts were also made to cripple grain production in Spain with wheat *fungus*, but without success.

Eleven Chinese cities were allegedly attacked during "field trials" using infectious agents including *Yersinia pestis*, *Vibrio cholerae*, and *Shigella*. These attacks may have backfired because up to 10 000 Japanese soldiers reportedly contracted *cholera* after a biological attack on Changde in 1941. As a result of the Japanese biowarfare program, 580 000 people are estimated to have died in China.

Vaccine research and development was conducted at both Tokyo University and Unit 731. By the end of the war, the Japanese biowarfare program claimed to have effective vaccines for *anthrax, cholera, dysentery, typhoid, and typhus*.

Polish physicians used a vaccine and a serologic test during World War II in a brilliant example of **"biological defense".** Knowing that inoculation with killed Proteus OX-19 would cause a false-positive Weil–Felix typhus test, Polish physicians inoculated the local population with a preparation of *formalin-killed Proteus OX-19* to create a serologic pseudoepidemic of typhus. Using serologic surveillance, the German army avoided areas that appeared to contain epidemic typhus; consequently, residents of these areas were spared by deportation to concentration camps.

Several reported but unconfirmed allegations indicate that Polish resistance fighters conducted biological warfare against Nazi occupation forces, including using letters contaminated with *Bacillus anthracis* to cause cases of cutaneous anthrax among Gestapo officials and using typhus against German soldiers.

The perceived threat of biological warfare before World War II prompted Great Britain to stockpile vaccines and antisera, establish an emergency public health laboratory system, and develop offensive biological weapons. "Cattle cakes" consisting of cattle feed contaminated with *B anthracis spores* were designed to be dropped from aircraft into Axis-occupied Europe to cause epizootic anthrax among livestock, which would in turn induce famine.

The US program. The US military recognized biological warfare as a potential threat after World War I. Major Leon Fox of the Army Medical Corps wrote an extensive report concluding that improvements in health and sanitation made biological weapons unfeasible and ineffective. In the fall of 1941, before the US entry into World War II, opinions differed about the threat of biological warfare. In 1951, the first biological weapons, anticrop bombs, were produced. The first antipersonnel munitions were produced in 1954, using *Brucella suis*. The United States weaponized seven antipersonnel agents and stockpiled three anticrop agents (see Table 5.1) in 16 years.

Table 5.1 – Biological agents produced by the US military (destroyed 1971–1973)

Lethal Agent	Incapacitating Agent	Anticrop Agent
Bacillus anthracis *Francisella tularensis* Botulinum toxin	*Brucella suis* *Coxiella burnetii* Venezuelan equine encephalitis virus Staphylococcal enterotoxin B	Rice blast Rye stem rust Wheat stem rust

However, the US military has never used biological weapons. The Central Intelligence Agency developed weapons using toxins including *cobra venom* and *saxitoxin* for covert operations; all records

regarding their development and deployment were destroyed in 1971. Most tests used simulants thought to be nonpathogenic, including *Bacillus globigii*, *Serratia marcescens*, and particulates of zinc cadmium sulfide.

Open-air releases of human pathogens (*Coxiella burnetii, Francisella [Pasturella] tularensis*) were remote Pacific Ocean sites to study viability and infectivity using animal challenge models. Controversial studies included environmental tests to determine whether African Americans were more susceptible to *Aspergillus fumigatus*, as had been observed with *Coccidioides immitis*. These studies included the 1951 exposure of uninformed workers at Norfolk Supply Center in Norfolk, Virginia, to crates contaminated with *Aspergillus spores*.

The first large-scale aerosol vulnerability test conducted in San Francisco Bay in September 1950 using *B globigii* and *S marcescens* demonstrated the public health issues of such testing. An outbreak of 11 cases of nosocomial *S marcescens* (*Chromobacterium prodigiosum*) urinary tract infection occurred at the nearby Stanford University Hospital; one case was complicated by fatal endocarditis. Risk factors included urinary tract instrumentation and antibiotic exposures.

5.3 Bioterrorism and germ warfare

Objectively, the likelihood of surviving a biological attack is much better than surviving a nuclear strike. Despite this, those who are unfamiliar with microbiology tend to find biological warfare very frightening and often regard it as more immoral than chemical or nuclear warfare. This disproportionate response to germ warfare can be seen in the hysterical response of the United States to the anthrax attacks of 2001–2002 that followed the terrorist destruction of the World Trade Center. The actual number of casualties was low, yet the associated fear was widespread and became a hot media topic. Perhaps one major reason for the fear is lack of visibility. Guns and bombs are highly visible. Infectious microbial agents are invisible to the naked eye. The fear of invisible dangers can become quite obsessive.

Whether or not research on germ warfare should be done is hotly debated. Knowing how to protect against an infectious disease inevitably provides information that would help in using the disease against an enemy. This conundrum is true in other areas. For example, the technology to build a nuclear power station is closely related to that needed to develop nuclear weapons. The same body of knowledge can often be applied to both positive and negative objectives.

Another issue is that of the Third World versus the industrial nations. Germ warfare has been described as the "poor man's nuclear weapon". Nations too poor to develop costly high-tech weapons could throw together crude biological weapons relatively easily and cheaply. Germ warfare thus represents a possible means by which Third World nations could protect themselves against the rich nations. This aspect is compounded by the fact that soldiers from rich countries have higher life expectancies and a better quality of living than do the poor inhabitants of the Third World. Thus a poor dictatorship might be tempted to release a biological agent within its own borders and accept casualties to its own people, knowing that this would frighten off a rich invader. There is some historical precedent for this. In World War I typhus epidemics were common on the Eastern front. The Serbians lost 150 000 men to typhus in the first 6 months of the war, including more than half of their 60 000 Austrian prisoners of war. Paradoxically, this actually aided the Serbs, because the Austrians were so frightened by the typhus epidemic that they kept their armies out of Serbia for fear of infection. Third World nations are also much more accustomed to death and illness due to extreme poverty. Perhaps this is one reason why the rich nations are so eager to ban germ warfare while keeping more expensive weapons of mass destruction in circulation.

Biocrimes. Biocrime refers to the malevolent use of biological agents when the perpetrator's motivation is personal, as opposed to a broader ideological, political, or religious objective. Although biocrimes constitute only a small fraction of criminal assaults and are usually unsuccessful, a well-executed attempt may be deadly; the resulting disease may pose clinical and forensic challenges. Biocrimes

have generally been more successful than bioterrorist attacks; 8 of 66 biocrimes reviewed by Tucker produced 19 deaths and 31 injuries.

Biocrimes are typically attempted by perpetrators with scientific or medical expertise or who have recruited suitably trained accomplices. One of the most striking examples of foodborne biocrime occurred in Japan between 1964 and 1966. Dr. Mitsuru Suzuki allegedly contaminated food items, medications, barium contrast, and a tongue depressor with *Salmonella typhi* and agents of *dysentery* on numerous occasions; these crimes resulted in over 110 cases of infection and four deaths.

A variation on the Suzuki crime occurred in 1996 when Diane Thompson, a hospital microbiologist, deliberately infected 11 coworkers with *Shigella dysenteriae*. Eight of the 11 casualties and an uneaten muffin tested positive for *S dysenteriae* type 1, identical to the laboratory's stock strain by pulsed-field electrophoresis.

Murders by direct injection included the use of diphtheria toxin in Russia in 1910 and *Y. pestis* in India in 1933. The director of a Norwegian nursing home was convicted in 1983 of murdering 11 patients by injecting them with a curare derivative. Biocriminals have also harnessed the most lethal emerging pathogen of the 10^{th} century; there have been at least four murder attempts by injecting victims with human immunodeficiency virus-infected blood.

5.4 Long-term biological problems

Many of the bioethics issues mentioned earlier are fashionable because of their technological novelty and seem likely to fade from public awareness relatively soon. What will mostly be left are underlying issues, such as access to health care and privacy, that apply both to new advances and to previous technology. However, there are several biological issues that are less romantic but may well be of more real importance. We will briefly mention these as a counterweight to topics such as human cloning.

Two centuries of advancing medical technology have increased life expectancy from the mid-thirties to the mid-seventies in the industrial nations. Infant mortality has dropped from nearly 50 % to less than 1 %. The result is a population explosion that is far more

hazardous to the planetary environment that any high-tech tinkering with nature. Although antipollution measures and recycling may help slightly, the growth of the human population inevitably consumes more resources and encroaches on the natural world.

Increased life expectancy also means that the average age of the human population is increasing. The ever greater proportion of old and retired people is putting a major strain on the health care systems of the advanced nations. Predictions of the coming collapse of American Medicare or the British National Health System are heard with increasing frequency. These trends are exacerbated by the high cost of much novel medical technology. In the United States some 20 % of expenditure is now in the general area of health care, and a vastly disproportionate amount is spent keeping old people alive for their last few months.

Another factor is obesity. More and more the inhabitants of the advanced nations are getting fatter. This causes major health problems, many of which, like diabetes, need expensive long-term treatment. Population growth means increased crowding. Modern transport has led to increased mobility. The combination of these two factors has resulted in the rapid spread of infections around the world. From major pandemics such as *AIDS* and *tuberculosis* down to lesser epidemics such as *cholera* and *West Nile virus*, there are ominous signs that infectious disease is making a comeback. At the same time we have the spread of genetic resistance: to antibiotics among bacteria, to antivirals among viruses, and to insecticides among the insects that carry many infections or ravage crops.

On the one hand, fending off novel or resistant infections is becoming ever more expensive in the rich nations. On the other hand, the spread of lethal infections is counteracting the population explosion to some extent in the poorer nations. This is especially evident in Africa, where actual population declines are predicted, largely as a result of AIDS.

Listing problems tends to create a gloomy atmosphere. So let us end by saying that most problems today are the problems of success. Western science is responsible for today's overpopulation precisely because it solved yesterday's problems of famine and disease. We

believe that technology will solve many of the new generation problems. The foregoing list of issues should be viewed more as a to-do list than a forecast of gloom and doom.

Questions for Self-checking

1. What are the main aspects of ethical problems dealing with infection deceases?
2. Why infections are important?
3. What main infection deceases do you know?
4. What countries did participate in biological weapons creation in the 19^{th}–20^{th} centuries?
5. Describe a role of Germany and the USA in germ warfare.
6. What biological agents were produced by the US military?
7. What does bioterrorism mean?
8. What does biocrime refer to?
9. List long-term biological problems.

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