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Bioethics controversies, laws and codes throughout history

INTRODUCTION

Three centuries B.C., Herophilus, founder of Alexandria's first medical faculty, is said to have practiced human vivisection on several hundred prisoners supplied by King Ptolemy[1,2], despite the teachings of Hippocrates.

On June 14, 2021, experts from the United Nations Organization (UNO) said they were "extremely alarmed" by reports of "pre-tendency organ harvesting" targeting minorities in detention in China[3]. This parallel raises the question of how the ethics of care and research have evolved over time. Research on living organisms (bio) and its results have regularly questioned individuals and societies. These questions could be moral, deontological or ethical. Although they share an etymology (mores in Latin and ethos in Greek mean morals), the terms moral and ethical do not have the same meaning. Morality can be defined primarily as "A set of rules of conduct based on a set of values and principles. These values and principles differentiate between right and wrong, justice and injustice. The word deontology comes from the Greek deon, "duty", and logos, "discourse, reason". Deontology can be defined as a set of rules (code), recommendations and duties that govern a professional's practice. Deontology and law are linked and evolve. Health law is based on a variety of legislative texts (patients' rights, bioethics, etc.) and is set out in codes (public health code, civil code, penal code, etc.). Ethics is often defined as an approach who questions moral principles and deontological rules, especially if these principles and rules do not answer a raised question[4].

According to Paul Ricœur, "rather than enabling us to discern between good and evil, ethics leads us to choose between several forms of good, or even the lesser evil. It is based on reflection, human qualities and openness "[5]. This active approach is based on debates that fuel collective reflection. These debates evolve and are present at both societal and individual levels. They punctuate scientific and media discoveries. Applied ethics involves a wide range of disciplines and players (doctors, lawyers, philosophers, etc.)[6].

Scientific controversies and scandals are prime opportunities for ethical debate. This didactic work has researched scandals and controversies in medical research from the Second World War to the present day, and parallels them with key moments in the evolution of laws and international codes of bioethics.

METHOD

The key moments in bioethics were chosen on the basis of definitions provided by the French Ministry of Solidarity and Health[7]. The table summarizes international and French key moments. Ethical controversies and scandals were identified for historical contextualization purposes, using the Medline®, Cairn® and Persée® databases. Grey literature was also used. This narrative review was carried out by two researchers, SM and XG, with a consensus search for the choice of exemplification. The keywords used were the titles of the laws or codes, for example: Nuremberg Code.

RESULTS

Nuremberg Code and Trial

The first of twelve trials

(December 9, 1946, nineteen months after the German surrender), the Medical Case incriminated 20 doctors and 3 scientists involved in medical experiments on human beings (Versuchspersonen). Among the atrocities committed, the authors have chosen to recount the experiments carried out at Ravensbrück, from July 1942 to August 1943.

Twenty-six inmates (mainly Polish) were deliberately injured (fractures and wounds) and infected in order to study the action of sulfonamides. Organ samples (muscles, tendons, bones) were taken. This research followed the death, in 1942, of SS-Obergruppenführer Heydrich, Himmler's right-hand man and himself head of Hitler's police force, of fulminant septicemia from a wound inflicted by a Czechoslovak resistance artillery bomb. Dr. Gebhardt, Professor of Surgery at the University of Berlin, SS chief clinician and Himmler's personal physician in charge of Heydrich, was blamed for not using sulfonamides. In order to clear his name in Hitler's eyes, Gebhardt conducted the Ravensbrück to prove the ineffectiveness of sulfonamides. After recovering a camera and some blank film from the luggage of the deportees, anthropologist Germaine Tillon and resistance fighter Anise Postel-Vinay immortalized the Versuchskaninchen, "Experimental rabbits "[10]. These photos and other archives have been deposited with the Musée de la Résistance et de la Déportation in Besançon by Anise Postel-Vinay [see photo].

At the trial, the defense pointed to the absence of any valid norm prohibiting experimentation on humans, to an analogy with American experiments, and to the vagueness of the Hippocratic oath. For the Nazis, the oath had nothing to do with research, and the development of knowledge justified exactions. Other arguments included the disinterest of researchers, the limitations of experimental animal models and the opportunity for inmates to atone for the crimes that had led to their internment.

Date	Text	Bioethical contribution
1947	Nuremberg Code	First written document on human research. Created by judges and jurors, it lays down 10 rules concerning biomedical research. Global in scope
1964	Declaration of Helsinki	Moral imperative written by WMA doctors. Establishes as a basic principle the primacy of the individual well-being of the research subject over the collective well-being.
1966	1st ethics committees	Birth of *review committes* in the United States and creation of bioethics research and training centers
1979	Belmont report	Prepared by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. Three principles: respect, beneficence and justice
1988	Huriet-Sérusclat Act	France's first legally binding text governing biomedical research
1993	International Bioethics Committee	A worldwide body created by UNESCO, made up of 36 experts responsible for overseeing progress in the life sciences and their applications, while respecting bioethical values.
1997	Oviedo Convention	First international legal instrument. Clarifies the issues surrounding genetics, organ donation and MPA.
1993	French bioethics laws and their evolution	Universal Declaration on the Human Genome and Human Rights
1997		Universal Declaration on the Human Genome and Human Rights
2003		International Declaration on Human Genetic Data
2005		Universal Declaration on Bioethics and Human Rights

Table 1 - Key moments in bioethics

This trial and the awareness has led to the development of the of the ration of ten rules, aka the Nuremberg Code, summarized in Appendix 1 online. The historical significance of this trial is considered to be at the root of the emergence of bioethics. The Nuremberg Code is the first international summary of the rules governing lawful experimentation.

Photo - Photograph of Basia, operated on 5 times in 1942 and whose wounds never healed.
Back in Poland in 1945, she enrolled at university, but died two years later of a sudden fever. © Anise Postel-Vinay.

In 1947, wishing to emancipate themselves from government institutions, physicians created an international confederation of national medical associations, independent of national governments: the World Medical Association (WMA). Its aim was "to ensure the independence of physicians and to achieve the highest standards of ethics and health care". As early as 1947, it reworked the Hippocratic Oath, in light of statements by Nazi doctors who believed they had respected it. In September 1948, three months before the Universal Declaration of Human Rights, the WMA adopted the Declaration of Geneva. This oath, conceived as an adaptation of the Hippocratic Oath to situations of human experimentation, has undergone several revisions, most recently in 2020. It is described in Appendix 2 online[8-12].

Declaration of Helsinki (Finland)

In 1956, the Grünenthal laboratory marketed thalidomide in Germany and gradually throughout Europe. It was proposed as a sedative and for the treatment of nausea and vomiting in early pregnancy. In 1961, an alarm was sounded, with a significant increase in the number of birth defects (several thousand cases of phocomelia: non-formation of the upper or lower limbs) in mothers who had used thalidomide during the first weeks of pregnancy. Animal testing (pregnant spleen) in 1954 revealed no particular toxicity. Human trials involved only a few hundred patients.

Clinical" or "non-clinical "non-clinical" trials were very limited,
and analysis of the risk of foetotoxicity was not mandatory.

The tha-lidomide case gave rise to the first European directive of 1965 (dir. 65/65), which introduced the definition of "non-clinical".

The directive defines the term "proprietary medicinal product" and establishes the principle of marketing authorization. The directive obliges member states to refuse authorization if the dossier is incomplete, if the product is considered dangerous or if proof of efficacy is insufficiently documented[13,14]. In 1964, the WMA drew up the "Recommendations for Physicians Carrying out Bio-medical Research Involving Human Subjects": the Declaration of Helsinki. The aim was to "enlighten the conscience of physicians throughout the world". Whereas the Nuremberg Code focused on the human being as the object of scientific research, the Helsinki Declaration sought to set out a code of conduct for medical researchers and others involved in bio-medical research.

The main principles were the reiteration of the importance of informed consent and the prevalence of the subject's well-being over the interest of science. The balance of benefit (principle of beneficence)/risk (principle of non-maleficence) was central. The Declaration of Helsinki clearly sets out the central issue in bioethics: how to ensure that research subjects' individual rights are protected, while seeking to improve the common good? This declaration saw its ninth version signed in Brazil in 2013. Developments have seen the inclusion of the use of placebos, which were initially forbidden, and the end of the distinction between the two "therapeutic" and "non-therapeutic researches "[15,16].

First ethics committees in 1966

In 1966, Professor Beecher, an anesthesiologist and resuscitator, compiled fifty examples of ethical errors regularity. Ethical issues mainly concern consent (present in 2 of the 50 examples cited) and the benefit/risk balance of the products or interventions used. He classifies the examples published in the New England Journal of Medicine into six groups. The first concerns the interruption of an effective treatment. He describes a trial in which the parenteral administration of penicillin to treat rheumatic fever was suspended. The administration of a placebo to these 109 patients resulted in acute rheumatic fever and acute nephritis. The second group concerns adverse drug reactions. It relates the administration of triacetyloleandomycin, responsible for liver dysfunction in juvenile delinquents detained in a center (including the mentally retarded) for acne. The third group covers physiological studies. It covers, for example, the search for the minimum dose of chloramphenicol leading to hematological toxicity. The fourth group concerns the improvement of knowledge of a disease. It relates the administration of azoted substances to patients suffering from cirrhosis, in order to induce a hepatic coma. The fifth group concerns the improvement of technique. It relates an experiment involving the introduction of a needle into the left atrium during bronchoscopy in patients without cardiac disease. The sixth group is described as bizarre by the author, with, for example, the practice of vesico-urethrography on healthy newborns in search of bladder reflux[17].

Against this backdrop of questioning and growing research funding, the U.S. Public Health Service set up the first review committees in universities. Their purpose was to respond to the inadequacies of codes of ethics, which were unable to answer certain complex questions.

In 1974, the State issued Order 45CFR46, which harmonized the decisions of ethics committees and stipulated that no research could henceforth be funded without the approval of an Institutional Review Board (IRB)[18]. At the same time, bioethics research and training centers were set up in American hospitals.

The Belmont Report in 1979

In 1979, in the United States, the National Committee for the Protection of Human Subjects in Biomedical and Behavioral Research published the Belmont Report. This report was published seven years after the Tuskegee scandal. From 1932 to 1972, doctors at the Tuskegee Institute studied the natural course of syphilis in a cohort of poor, analphabetic black patients from Alabama. By participating in this study, these "subjects" received hot meals, free medical examinations and a free concession if they agreed to an autopsy. In 1947, penicillin became the standard treatment for this infection, and despite this standard, the "subjects" in this cohort did not receive this treatment. The consequences were serious: 28 deaths, 100 cases of complications, 40 infections in wives, and 19 discharged syphilis[18,19]. The study, initially scheduled to last six months, continued for forty years. In 1976, in his defense, the director of the Tuskegee Public Health Department stated that the "subjects" were not patients, but "clinical material". In 1997, Bill Clinton apologized for forty years of experimentation. The Belmont Report, published seven years after the end of the experiment, was intended to analyze the ethical problems encountered in research involving human subjects. The first part of the report interroves the boundaries between the practice of medicine and research. The second part sets out three fundamental ethical principles of research: the principle of respect for the person, beneficence and jus- tice. The principle of respect implies recognizing autonomy and pro- tecting people whose autonomy is diminished. The principle of beneficence implies doing no harm: maximizing benefits and minimizing potential harm.

The principle of justice is defined broadly: injustice exists when a person is denied certain benefits to which- he or she is entitled without good reason, or when a burden is imposed excessively. Research must not systematically disadvantage certain categories of people. The third part stresses the importance of consent based on information, understanding and voluntariness. It recalls the im- portance of systematic evaluation, the nature and extent of risks and benefits. It addresses selection at both societal and individual levels. Individual justice calls for fairness: researchers cannot, for example, select relatives for research expected to be highly beneficial and prisoners for research involving many risks. Societal justice requires a distinction to be made between categories of subjects who can or cannot withstand an experimental pro - tocole. For example, it seems fair to prefer adults to children, or to avoid including the mentally ill. This report was to become the benchmark for bioethical principles[19,20].

Huriet-Sérusclat Act in 1988, revised in 2004

In 1988, Prof. Milhaud, head of the polyvalent intensive care unit at the Amiens Regional Hospital, had one of these brain-dead patients inhaled alternately nitrous oxide and oxygen. The aim of this experiment was to provide scientific support for the Poitiers trial, in which an inversion between nitrous oxide and oxygen was suspected of being responsible for the death of a 34-year-old woman during an operation on the parotid gland. The film of this experiment was revealed to the public at the Poitiers trial. The audience was stunned. The young man's family had never been informed of this experiment. Prof. Milhaud was acquitted, since he could not be charged with the offence of intentional assault and battery, which presupposes that the victim is alive, but he was reprimanded by the Ordre National des Médecins, despite an appeal to the French Supreme Court, since "the fundamental deontological principles which apply to the doctor in his relations with his patient do not cease to apply with the death of the patient "[21, 22].

Twenty-four years after the Helsinki declaration, the Huriet -Sérusclat law on the protection of persons undergoing biomedical research was promulgated. Its aim was to protect people who undergo clinical research studies. The Declaration of Helsinki defined: 1) the need for an experimental protocol submitted to an independent committee; 2) the need for a careful assessment of the foreseeable risks and benefits of the research for the individual prior to the commencement of the research, the individual being able to be healthy or ill; 3) the need for accurate publication of research results; 4) the principle of free and informed consent. Huriet and Sérusclat enshrined in law what was a "moral injunction "[19]. The duty to provide information, to obtain consent, now takes the form of a written document. Research-related risks are covered by a specific insurance contract. Clinical research projects are subject to the opinion of an advisory committee for the protection of individuals in biomedical research (CPP). Projects include a sponsor and a principal investigator. They are declared to the relevant supervisory authority by means of a letter of intent. The promoter is the individual or legal entity who assumes legal responsibility for the project.

The public institutions, nonprofit organizations, for-profit organizations (pharmaceutical industry) or even an individual can be a sponsor. The investigator is a physician who directs and supervises the research and assumes scientific responsibility[23,24].

The International Committee Bioethics Committee (CIB) in 1993

On March 4 1982, a few days after the birth of Amandine, "the first test-tube baby", Prof. Frydman, Dr. Testart, jurist Labrusse, Father Thévenot and Prof. Rosa were invited to appear on a public television program with the catchy title: "L'après-Amandine: faut-il changer la morale? In vitro fertilization puts the limits of science back at the center of debate, and raises numerous ethical questions, such as the legal status of the embryo. In 1983, France became the first country to set up a national ethics committee. The role of the Comité consultatif national d'éthique (CCNE) is to provide advice and assistance on societal issues and ethical problems that may arise from advances in science, biology and medicine[24]. Other countries subsequently set up their own national bodies. Given the variety of ethical opinions (themselves secondary to the country's intrinsic factors), legislation and jurisprudence, the need, if not for consensus, then at least for international harmonization is self-evident. It was with this in mind that the International Bioethics Committee (IBC) was set up in 1993 by the Director of UNESCO (United Nations Educational, Scientific and Cultural Organization), Mayor Zaragoza. The IBC is made up of 36 independent experts, and is the only global body for reflection on bioethics. In 1997, it published the Universal Declaration on the Human Genome and Human Rights. The box (available online) summarizes the six parts of the declaration.

Part A and its four articles define the human genome and recall that every individual has the right to respect for his or her dignity and rights, whatever his or her genetic characteristics. Part B reiterates the principle of risk-benefit assessment, free and informed consent, and the right to be informed (or not). It also reiterates that no-one should be discriminated against on the basis of their genetic- characteristics. Part C reminds us that research must respect human rights and human dignity. The aim is to alleviate suffering and improve the health of the individual and of humanity as a whole. Part D notes the importance of rigor, prudence, intellectual honesty and integrity, as well as multi-disciplinarity, in the conduct of their research and in the presentation and use of their findings. Part E recalls the need to respect and promote active solidarity with individuals, families or populations particularly vulnerable to genetic diseases or disabilities. Part F asks States to promote this declaration.

The IBC published the International Declaration on Human Genetic Data in 2003, and the Universal Declaration on Bioethics and Human Rights in 2005 in appendix 3 online[25-27].

The 1997 Oviedo Convention (Spain)

The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, otherwise known as the Oviedo Convention, is the first coercive international legal instrument. Its main aim is to protect not only man as an individual, but also humanity as a whole. It follows on from the declarations of the International Ethics Committee, this time with the possibility of sanctions.

It prohibits any form of discrimination against a person on the basis of his or her genetic heritage, and authorizes predictive tests for genetic diseases for medical purposes only. Interventions on the human genome may only be undertaken for preventive, diagnostic or therapeutic reasons, and if they are not intended to introduce a modification in the genome of the descendants. Medically assisted reproduction techniques may not be used to select the sex of the unborn child, except in order to avoid a serious hereditary disease. It prohibits the creation of human embryos for research purposes, and in countries where in vitro embryo research is permitted by law, the law must ensure adequate protection of the embryo. The Convention prohibits the removal of non-regenerative organs or tissues from a person who does not have the capacity to consent. It recognizes the importance of public debate and consultation on these issues. The provisions of the Oviedo Convention have been developed and supplemented in additional protocols relating to specific areas concerning the prohibition of human cloning, organ transplantation, bio-medical research and human genetics[28].

The main French bioethics laws since 1994

The first French bioethics law dates back to July 1, 1994. It laid down the rules for the legal and administrative handling of nominative health data. The two laws of July 29 set out three ethical principles: anonymity, free access and compulsory consent.

On July 7, 2004, a law was passed to complete the previous legislation, in particular by establishing a legal framework for cell therapy. It created the Agence de la biomédecine, prohibited the cloning of a living or deceased human being, and set out the limited framework for research on human embryos.

The 2011 law authorizes cross-donation of organs in the event of incompatibility between relatives, and the freezing of oocytes.

The 2013 law provides a framework for research on embryos (banned in 2004) and human embryonic stem cells. It stipulates that research may be carried out on supernumerary embryos conceived in the context of medically assisted procreation (MAP), which are no longer the subject of a parental project, after the couple concerned has been informed and given written consent.

The law of August 2, 2021 relaxes the legal framework for research on human embryo and embryonic stem cells. It authorizes female couples and unmarried women to benefit from AMP. It also authorizes the "self-preservation" of gametes with a view to subsequent MPA. Children born as a result of MPA have a right of access to non-identifying information about the donor. The framework for human embryonic stem cell research has also been modified, moving from an authorization system to a prior declaration system[29].

DISCUSSION

Main results, news and new questions of bioethics

The aim of this didactic work was to draw parallels between scandals and controversies in medical research from the Second World War to the present day, and key moments in the evolution of laws and international codes of bio-ethics. These various controversies help us to understand the importance of clear information, the basis of voluntariness and consent, and the ethical principle of respect for the individual, which requires recognition of personal autonomy. Autonomy has been flouted in the history of medical experimentation from the Versuchskaninchen at Ravensbrück to the Tuskegee scandal in Alabama.

They also help the reader to question the principle of appropriateness and the benefit/risk balance of an intervention. Examples of the discontinuation of treatments known to be effective, such as penicillin for rheumatic fever, or the use of active ingredients known to be dangerous, such as the administration of nitrogenous substances to patients suffering from cirrhosis, illustrate these two principles. The principle of justice has been described through injustices, such as the administration of triacetyloleandomycin despite knowledge of its hepatic risks to delinquent children detained in centers to treat acne.

Despite these organizations and laws, recent experiments on human beings have not respected ethical principles. In 2018, the Hong Kong symposium plunged the world into intense ethical reflection following the news of the birth of twins genetically modified in the embryonic state. The CRISPR-Cas 9 technique, a kind of the "biological scissors" technique used by Dr. Jiankui was designed to bring about the D32 mutation (found in 10% of the population), which inactivates the CCR5 (C-C chemokine receptor type 5) gene. This gene produces the CCR5 cellular co-receptors on the surface of CD4+ T lymphocytes, necessary for binding the human immunodeficiency virus. This experimentation on embryos does not comply with European, U.S. and possibly even Chinese law. Parental consent was obtained without the consent form or study protocol having been submitted to and approved by an ethics committee[30,32].

These experiments are not confined to countries where democracy is being called into question, such as China, with its genetically modified twins and so-called organ pre-harvesting targeting minors[3]. In France, an unauthorized clinical trial was conducted in an abbey near Poitiers in 2019. The Agence nationale de sécurité du médicament et des produits de santé (ANSM) banned this clinical trial illegally conducted by the Josefa fund in patients suffering from Parkinson's, Alzheimer's and other neurological diseases. Transcutaneous valentonine and 6-methoxy-harmalan devices were tested on over 350 people. The alleged investigators were Prof. Joyeux and Prof. Fourtillan, president of the Josefa[33] fund.

Limits and strengths

The authors have chosen the key moments in bioethics based on the definition provided by the French Ministry of Solidarity and Health[7]. This definition is debatable, and other key moments could have been presented, such as the Convention for the Protection of Human Rights and Fundamental Freedoms, published in 1953 by the Council of Europe, or the European Medical Charter - principles laid down from 1987 to 1995 by the European Council of the Order of Physicians. This work was carried out by two general practitioner researchers. The presence of historians, sociologists, philosophers, scientists specializing in the human sciences, members of civil society and members of patient associations would probably have led to different choices of examples. It would be enriching if this work could be continued and fleshed out in a multidisciplinary way.

The main strength of this work is its originality, particularly for medical researchers.

Outlook

This work serves as the basis for a course given to students enrolled in the health access program at Saint-Étienne. Discussions of consent, autonomy, justice, beneficence and non-maleficence guide doctors in their day-to-day practice.

Summary

Introduction. From ancient times to the present day, experimentation on living organisms, and on human beings in particular, has raised numerous moral, deontological and ethical questions. Applied ethics (bioethics, medical ethics, etc.) involve many different players (doctors, lawyers, philosophers, etc.). Controversies, even scientific scans, are privileged occasions for ethical debate. This didactic work has researched scandals and controversies in medical research from the Second World War to the present day, and compared them with key moments in the evolution of laws and international bioethics codes.

Method. Key moments in bioethics were selected on the basis of definitions provided by the French Ministry of Solidarity and Health. Ethical controversies were identified for historical contextualization purposes, using Medline®, Cairn® and Persée® databases and grey literature.

Results. Nazi experiments, the thalidomide scandal, Beecher's publication of 50 examples of non-compliance with research ethics, the Tuskegee scandal, the Milhaud affair, and the "test-tube baby Amandine" raised many ethical questions, and were followed by reference texts and the creation of organizations encading bioethics: the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the first ethics committees, the Huriet-Sérusclat law, the International Bioethics Committee, the Oviedo Convention and the French bioethics laws.

Discussion-conclusion. The exemplification of ethical principles can guide a physician in care and research.

➜ **keywords**: ethics; disagreements and disputes; history.

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