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Medical Research on Human Subjects – Historical Landmarks

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Abstract: *Medical clinical research, otherwise defined as research on human subjects, represents the standardized method unanimously accepted by the medical, scientific community, as well as by civil society, as the only way that allows the approval of the use in medical practice of a new drug, as well as of a new method of investigation or treatment. We will briefly present the history of medical research, with reference to Hippocrates, Galen, Avicenna, Ambroise Paré, James Lind, Edward Jenner, Pasteur, as well as about the negative examples and errors that manifested themselves in the name of medical research, from the perspective of medical ethics.*

Keywords: *research ethics, bioethics, history of medicine, Hippocrates, Galen, Avicenna, Ambroise Paré, James Lind, Edward Jenner, Pasteur.*

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Introduction

Medical clinical research, otherwise defined as research on human subjects, represents the standardized method unanimously accepted by the medical, scientific community, as well as by civil society, as the only way that allows the approval of the use in medical practice of a new drug, as well as of a new method of investigation or treatment. We are in the era of randomized, multicenter, international clinical trials, trials involving multidisciplinary teams around the world and in which the number of investigated subjects is in the thousands. These trials mobilize consistent financial and human resources, which is why no aspect is neglected, starting with the launch of the working hypothesis and until the publication of the results, the quality of work of all those involved in these processes will depend on the subsequent course of a new medication and, of course, the benefits for the population of future patients. In fact, today's therapeutic approach largely conforms to the concept of evidence-based medicine, the practitioner having the task of integrating evidence into the system of values and interests of each individual, tending towards the goal of personalized medicine and achieving the natural balance between what science offers and what meets the needs of each patient. Current clinical research is the result of a long process that has been defined and continuously evolved, benefiting from the contribution of technological development, development that has provided tools that have facilitated the achievement of a level of rigor and accuracy unimaginable fifty years ago. During this time, medicine has constantly responded to new and new challenges, always pursuing the same objectives, namely protecting the life and health of mankind, alleviating suffering and controlling diseases.

The novelty element that we bring in this text is to briefly present the history of medical research against the background of the relationship with medical ethics.

Early life

Since ancient times, those who have discovered their calling to alleviate the sufferings of their fellow human beings have had to face countless challenges, most of them generated by the lack of methods and means necessary to establish a correct diagnosis, as well as by extremely limited therapeutic resources. Myths and superstitions dominated the spiritual and intellectual life, providing the only answers as to the causes of disease, and most mythologies had a medical god, diseases being attributed

to the will and whims of the gods, so that, in the face of human helplessness, only a being endowed with supernatural powers, a superior entity, could have access to the mysteries of the universe.

It took thousands of years before humanity began to look for the causes of everything in its own world, looking around and analyzing. The need to search, to research, has always accompanied humanity, but deciphering the mysteries of the universe, including the complex universe of the human being, has been a long and difficult road, which humanity has crossed step by step, removing obstacle after obstacle. As for the engine that spurred the human spirit to explore into the unknown, it is made up of two "components": curiosity and necessity.

Curiosity is a natural attribute of intelligent beings, with which they integrate by adapting to the environment or, in the case of humans, adapting the environment to their own needs (Hands, 2019, 519). In terms of necessity, let us not forget that our species appeared and developed in a hostile environment, full of dangers at every turn, an environment where cold, lack of food, poor hygiene, wild animals or even other individuals could hurt, cause disease, suffering, death. It is also important to note that all the information we have today has been obtained over time through tools that, by lengthening our senses, managed to help us penetrate beyond the accessible sphere through our natural abilities, while our ancestors had to open the gates to knowledge one by one and with great effort.

Without claiming that all the remarkable episodes in the history of medical research have been exhausted, we propose a review of names and events that marked the evolution in time as openers of new horizons.

Hippocrates of Kos (460–375 BC)

He belongs to the gallery of great spirits of Greek antiquity, along with Socrates, Plato and Aristotle, being awarded the title of father of medicine, thus honoring his contribution to the emergence and development of the medical profession, a field at the border between science and art, ennobled by love and devotion for suffering fellows. He was born in 460 B.C. on the Greek island of Kos into a family of physicians and followed the family tradition in an era when knowledge was passed down from generation to generation. He separated medicine from religion and philosophy, defining its field of activity and the notion of doctor, but emphasized, both in his works and by personal example of conduct in relation to the patient and his family, the importance of ethics in medicine.

He worked both in the care of the sick and as a master, establishing the first medical school so that information would be accessible to all those

who wanted to join this profession, the master keeping something of his paternal attitude in relation to his disciple.

As a physician, his ideas revolutionized the approach to diseases, to which Hippocrates attributed natural causes, generally related to the environment in which the patient lived and his way of life, an idea whose validity is preserved even today, and he paid special attention to the discussion with the patient and his family (what we call today anamnesis), as well as thorough clinical examination. He recommended that his disciples write down everything they observed so that other doctors could know the case and encouraged discussion and collaboration among colleagues.

In the absence of effective remedies, most therapeutic recommendations referred to diet to restore balance in the body, which we can still apply today in quite a few cases. Sensing the danger of medicine moving away from its humanistic purpose and character, as well as the risks resulting from the use of insufficiently known remedies, Hippocrates elaborates the famous *Oath*, a text considered the first code of ethics of the medical profession. Generations of doctors have spoken, with emotion, the wise words of the "father of medicine", achieving a communion of ideas and feelings that define the unique character of the medical profession.

If we were to synthesize the main concepts of the Hippocratic doctrine, we would identify the following: the role of environmental factors in triggering diseases but also in curing them, the integrality of the human body and the balance necessary to preserve health, the role of observation, anamnesis and clinical examination in establishing the diagnosis, noting observations and collaboration between colleagues, keeping secrecy and decency in relations with the patient and his family, avoiding overstepping skills so as not to do more harm than good.

On the imperative to do no harm, certain observations are required. From the start, the doctor's intention is to help, to comfort, thus to do good, this desideratum is included in the very definition of the profession. However, by applying improper treatment on the basis of a wrong diagnosis, anyone can, as a doctor, harm an already suffering person. As for the intention to do evil, using her knowledge for this purpose, she is rejected from the start, and *the Oath* mentions this aspect. He left to posterity sixty-seven works under the title of *Corpus Hipocraticum*, works in which his doctrine is found and which served as inspiration for other great spirits of medicine in the following centuries.

The message of Hippocrates is a deeply humanistic one, speaking about a profession practiced by honest people in relation to patients, their family and other doctors, meticulous in observing and recording

observations, willing to transmit information to be used by other colleagues or future generations and, last but not least, a profession in which the ability to empathize with people's sufferings is truly embodied by its servants. Thus, debunking medicine is equivalent to making those who practice it responsible and imposing from the beginning the two categories of values that are still found today, namely the values of knowledge and the values of morality (Iftimovici, 1994, 56-64; Iliescu & Dinulescu, 2003, 78-84).

Claudius Galenos (Galenus) 129-216 AD

Born in 129 AD in Pergamum (Greece), Galenus continued the Hippocratic tradition in medicine, but also made a valuable contribution to the progress of knowledge, being considered the first pharmacist, the one who laid the foundations of the preparation of medicines, a step forward from Hippocratic medicine that generally used diet and natural remedies to treat diseases.

Connoisseur of the works of Plato, Aristotle and Hippocrates, Galenus practiced dissection on animals, being a follower of the experimental method in acquiring knowledge (Iftimovici, 1994, 71-74; Iliescu & Dinulescu, 2003, 102-106), considering that experience must be the basis of knowledge (Iftimovici, 1994,71 sq). In this context, one can mention the famous Galenic axiom according to which the sick on whom a remedy will have an effect will recover, unlike those on whom it will have no effect and who will inevitably die.

Avicenna – Arab prince of medieval medicine (980–1037 AD)

The so-called and greatest scholar of the Muslim world was born in Central Asia in 980 AD, his original name being Abu Ali al-Husayn ibd abd Allah ibn Sina. Connoisseur and admirer of the great spirits of ancient Greece, speaking especially of Aristotle and Hippocrates, Avicenna's legacy transcends centuries, his works being studied in medical universities from the Middle Ages, until almost the modern era.

Thus, in the "Canon of Medicine", the Arab scientist talks about the need to test the proposed remedies first on animals, then on humans, and only those remedies that have proven effective to be used. He also talks about simple diseases and complicated diseases, admitting that treating a patient with several conditions is not exactly simple, which today's doctors know very well when they have to take into account all the comorbidities and drug interactions that a patient may present. According to Avicenna, knowledge must be obtained on the basis of intuition, experiment, and intellect. Today, when we speak of "evidence-based medicine," it behooves us to honor one of

the most brilliant spirits of his time: Avicenna, who fully deserved the title of "the greatest scholar of the Muslim world" (Iftimovici, 1994, 103).

Ambroise Paré (1510–1590)

Self-taught as a genius (Iftimovici, 1994, 141), Paré was considered the father of modern surgery due to his innovations in this field and the dedication he showed throughout his career. He was born in 1509 or 1510 and began practicing as a barber, then served as a surgeon in the army. The year 1537 finds him at the front, tending to wounds caused by firearms, relatively recently introduced into the practice of warfare (Iftimovici, 1994, 141-143).

At that time, the procedure used was burning wounds with hot oil, a method both painful and ineffective, as a result of which the wounds became infected and most of the wounded died. At some point, due to supply difficulties in wartime conditions, the surgeon found that the oil had run out, and he had to find an alternative solution. Thus, he used a mixture consisting of egg white, rose oil and turpentine, materials at his disposal. He applied this mixture to the soldiers' wounds and waited, anxious, unable to sleep for fear that the young soldiers might die because of the way he had treated them. The next day, however, he was surprised to find that those to whom he had applied his mixture felt better, had not developed a fever, the pains had improved and even the wounds looked better. We could consider this the first experiment in the field of surgical methods, in light of the fact that something new, unknown to current practices, was used, which also caused the surgeon to worry about the possible unfavorable evolution of the wounded treated in this way. Applying the principles of Hippocratic ethics, Pare strove and hoped not to harm the wounded whose suffering was already great in the first place. The man who had difficulties in his career and was mocked by his confreres for failing to learn Latin had special merits in the emergence and development of surgery as a distinct field of medicine. However, maintaining his modesty throughout his life, he used to say: "I bandaged him, God healed him" (Tanner & Weissler, 2017).

James Lind (1716–1794)

If the Frenchman Ambroise Paré is considered the father of surgery, the Englishman James Lind (1716-1794) is credited with the first clinical trial in the history of medicine, a trial conducted on board a maritime ship. As a consequence of the great geographical discoveries of the XV - XVI centuries, navigation routes expanded, merchant fleets crossing the world's oceans, connecting the old continent with the New World.

These new opportunities contributed substantially to the economic prosperity of European nations with merchant fleets and access to the ocean, but also generated serious health problems among sailors, the most famous and at the same time the most serious being scurvy. This suffering diminished much of the sailors' ability to sail and resulted in more serious cases, even death.

It is now known that the origin of this condition is vitamin C deficiency, whose chemical formula was discovered only between 1928 and 1933, but at that time the level of knowledge was much more limited. However, the experience of seafarers, especially long-haul seafarers, had shown that the disease occurs mainly and develops severe forms in cases where calls for the supply of fresh food, especially fruit, were difficult or even impossible, as they could not be stored for a long time due to their perishability. For this reason, when the mariners' diet consisted exclusively of preserved foods, for example salted and smoked meat accompanied by rusks, possibly 'sprinkled' with alcohol, scurvy inevitably appeared on board.

In 1747, while James Lind was aboard Salisbury, some of the crew were already showing symptoms of the disease, and the doctor decided it was time to check the information on the role of citrus fruits in preventing and treating scurvy in an experiment in which the subjects were obviously the sailors in his care. Lind divided the 12 crew members into groups of two and introduced two oranges and one lemon into their daily diet, while the rest of the group received other foods. After a while, he found that the sailors who had received citrus fruits showed obvious signs of improvement, while for the others nothing had changed. Based on the results of his experiment, James Lind recommended to British naval authorities to supply transoceanic ships with citrus fruits, which was regulated a few years later (Lind, 1753). If we were to analyze Lind's experiment from the perspective of today's trials, we could see that the English doctor carried out what today we would call "randomization", his intention being from the beginning to verify the beneficial effects of citrus intake in combating scurvy, comparing the different evolution of his "subjects" depending on the chosen variable. respectively, diet. To verify this hypothesis, let's note that some of the sailors were subjected to an unhealthy diet, which could lead to worsening of their condition or even death. In the absence of ethical regulations, James Lind acted according to his own expertise and inspiration, and the results of his work later proved their usefulness.

Edward Jenner (1749–1823)

In an era when the etiology of infectious-contagious diseases was unknown and they posed a real threat to public health, especially during epidemics, an English doctor capitalizes on a millennial experience and gives it scientific value, practically opening a new era in medicine. His name was Edward Jenner. Practicing medicine in a farming community, Jenner was dealing with smallpox, a serious infectious-contagious disease with a mortality rate of around thirty percent of patients and resulting in serious and irreversible sequelae for survivors (scarring disfigurement is the best-known long-term effect of this disease, but blindness could also occur if the lesions damaged the structures of the eye, or the inability to use a limb if the lesions concerned their structure).

The cause of smallpox was unknown at the time, which explains why no cure was effective. Individuals with solid natural resistance survived (the term immunity was not in medical parlance at the time) and, importantly, they never went through the disease again. Today we have a lot of information about both microscopic and inframicroscopic pathogens, as well as about the evolution and response mechanisms of the organism to their aggression, but in the eighteenth century it was not even known about their existence, much less was their involvement in causing diseases.

Over time, people had tried with some success to limit the spread of the disease by resorting to various procedures called variolation, basically inoculating a healthy individual with attenuated virus by using objects belonging to smallpox patients, objects containing small flaky fragments from the surface of skin lesions. It was known and practiced by the ancient Chinese as well as in the Ottoman Empire, from where it was brought to England by Lady Mary Montagu, wife of the English consul who had smallpox as a child. But Dr. Jenner approaches another way of preventing smallpox, drawing on the experience of English farmers, a method that will prove safer and more effective than variolation and will be imposed, later adopted by science and medical practice. Thus, in the rural community served by Jenner, people had noticed the existence of two similar eruptive diseases, namely *small pox*, with severe evolution and *cowpox*, with much milder evolution. It was also well known that people who came into contact with sick cows and developed the rash on the palms did not get human smallpox. On an intuitive level, it could be said that cow disease had a protective effect on man.

Remembering the words of a well-known surgeon at Saint George's Hospital in London, John Hunter, Dr. Jenner decides instead of speculating, to try experimenting. As a true scientist, he brings together the elements

necessary for the experiment, starting from an unsolved problem, namely the disease without effective treatment, with epidemic evolution, adding observations on the similarity between the two eruptive diseases and the fact that the milder disease seemed to confer protection against the more serious disease and, wishing to verify this supposition, chooses a subject to investigate in the person of James Phipps, an eight-year-old boy, the son of his gardener. In order to verify this hypothesis, he will use biological material harvested from a fresh lesion on the hands of milker Sarah Nelmes, which he will inoculate by scratching the skin of the boy's arm. For nine days, according to the doctor's close supervision, the little subject felt slightly ill, developed the milker-specific palm rash, and on the first of July Jenner inoculated him with biological material containing the human smallpox agent that had been harvested from a smallpox patient. We can see that this was the riskiest moment, because if the doctor's hypothesis about the protective role of cow disease had not been confirmed, or if something had not worked, the child would have been in danger.

But Jenner's reasoning turned out to be correct, so James remained healthy, except for inflammation of the axillary lymph nodes and a febrile episode (today we know that these symptoms are related to the timing of antibody production), and the doctor's hypothesis was confirmed. Thus, although we cannot speak of an *actual trial* because it was not applied to a group, the experiment conducted by Edward Jenner has great scientific value, being the first truly significant step towards the eradication of smallpox worldwide, as well as other infectious diseases, since his method inaugurated the era of prophylaxis by immunization, and researchers in the following centuries will continue on the path opened by their English colleague who, Despite his successes and recognition from the medical community, he remained the same modest and benevolent man until the end. From an ethical point of view, we could make some observations about Jenner's experiment on little James, but only from the perspective of the criteria that guide medical research today, with all the regulations regarding the participation of minors as subjects of investigation and the risk to which they may be subjected, and not to omit the obligation to obtain an informed agreement from his parent, where applicable, the legal representative of the minor. If we were to refer to the risks in this case, let us remember that smallpox was a serious disease, so all members of the community, especially children, were at risk of disease and either die or remain with sequelae for life. Under these circumstances, we can accept that between contracting human smallpox unprotected and coming into contact with the disease following immunization by vaccination, the risk is significantly higher in the former. If further validation of his proposed

method and moral integrity was needed, Dr. Jenner did not hesitate to vaccinate his own son (Iftimovici, 1994, 174-175).

Nineteenth century

The fascination of the world seen under a microscope

In the history of medicine, the nineteenth century represents a preamble to clinical research that will explode in the next century, characterized by valuable contributions to the development of science in general and medical in particular, achievements attributed to solitary spirits working in personal laboratories, benefiting from technological discoveries in the field of optics, the optical microscope being the main working tool as well as the innovation represented by synthetic dyes, result of the development of chemistry and chemical industry.

Medicine and medical research are going through an intense period, in which great discoveries are taking place in laboratories, because it has become clear the need to extend the human senses to enter the microuniverse of the human body and microscopic beings, where centuries-old problems have found answers in which humanity has fought an unequal battle with infectious diseases, generating epidemics that have decimated the population of Europe. It can be said that, to a certain extent, medical research left man for a time, as the main subject of investigation, but everything discovered during that period in the fascinating world revealed by the magnifying power of the microscope will prepare medicine and medical research for the accelerated progress it will experience in the next century.

The most prominent exponent of this period remains the French chemist and biologist Louis Pasteur (1822-1895). Founder of microbiology, Pasteur studied microorganisms involved in various processes in nature, for example fermentation, offering the beer, wine and milk industries solutions to avoid food spoilage. At the same time, he also tackled pathogenic microorganisms, focusing on obtaining the anthrax and rabies vaccine. If in the case of anthrax, a disease caused by a bacterium, he managed to identify the pathogen under a microscope, as far as rabies was concerned this was impossible, being a virus, an inframicroscopic entity that could be visualized only in the next century with the help of the electron microscope. In the fight against the invisible adversary, Pasteur capitalized on the observation that the causative agent of rabies settles in the nervous system and began research into a vaccine using the brains and marrow of laboratory animals infected with rabies virus.

Three years after rabies research began, he was asked to administer the insufficiently elaborated and tested results of his work to a nine-year-old boy, Joseph Meister, who had been bitten by a rabid dog and whose mother begged the researcher desperately to save her son. If we were to analyze the case by referring to the rigors that regulate clinical medical research today, and the fact that we are talking about a child amplifies the ethical and legal implications, we would first ask ourselves to what extent the risk to which the little patient was subjected was justified, but it must be taken into account that rabies is still today a disease for which there is no cure. This leads to the conclusion that the scientist opted for the only alternative that would give the child a chance at survival, the risk mentioned above being assumed by both the child's mother and the researcher and no suspicion can be raised to the good intentions of the scientist in this case.

Along with Pasteur, we should mention the name of the German scientist Robert Koch, who, at the end of the nineteenth century, identified the formidable pathogen of tuberculosis, this discovery being the reference point in the efforts to eradicate this disease. Knowledge about microscopic organisms that inhabit our living environment and which, entering our body, can make us sick have led to the identification of methods to prevent and combat them through physical and chemical methods, methods that, applied in hospitals under the name of asepsis and antisepsia, have led to a significant decrease in mortality in surgery and maternity wards. Practically all the discoveries behind the microscope lens have subsequently served clinical research and identification of effective methods to prevent and combat infectious diseases, proving to be of wide applicability in medical practice (Iftimovici, 1994, 208-214; Iliescu & Dinulescu, 2003, 295-299).

Progress at any cost

Some research conducted at the end of the nineteenth century was the example of an exclusively utilitarian approach, to the detriment of respect for the individual and his rights, an approach reminiscent of the "principle" according to which the end justifies the means, which, obviously, in medicine contradicts ethics. Thus, an illustrative case is Jansen's smallpox studies, conducted in 1899, using as subjects a number of orphaned children from Foundling House, the reason invoked being that "calves were too expensive". Another example is that of the American gynecologist Marion Sims, nicknamed "the father of gynecology" due, of course, to her contribution to the development of this specialty, but who proceeded in an unethical manner when experimenting on black women, slaves, obtaining consent from their masters. We can also mention the case of the researcher

Albert Neisser, who between 1892 and 1898 tried to obtain a cure against syphilis (this disease could be defeated only after the discovery of penicillin), his subjects were prostitutes who were not asked for consent and, moreover, the result of the study was null, which means that the participants had no benefit (Hostiuc, 2022). The examples can continue on this topic, in which certain researchers wanted to achieve remarkable results and to chart new directions in medicine, a commendable intention, moreover, but for which the lives of subjects at risk were worthless, which from an ethical point of view is unacceptable, if we were to refer only to the Kantian imperative to treat all humanity as a goal, not as a means, not forgetting the Christian morality, according to which all men are equal before God. If we are to find a positive consequence from the above, it would be that the disclosure of these cases contributed to the redefinition of ethical and legal norms applied to clinical research.

Twentieth century – lights and shadows

Since the turn of the century, advances will be made in medical science, with research providing effective solutions against infectious diseases, and chronic diseases such as cancer, cardiovascular or mental illnesses will also be addressed. The era of singular researchers, such as Pasteur and Koch, mentioned above, had not ended, but the research institutes in which they would work had already appeared, being later supported by medical institutions, universities or authorities (Astărăstoaie & Trif, 1998, 86), a sign that, within society, the concern for the health of the population was increasingly accentuated and, at the same time, the role of research in the development of medicine was recognized. However, neither the working methodology nor the moral aspects are clarified, although as early as 1915 Yule spoke of the need for randomization (Pocock, 1983), after Louis referred as early as 1834 to the use of statistical analysis of results. It became increasingly clear the need to enroll a sufficiently large number of participants to ensure statistical significance, but, as these aspects were not yet sufficiently defined, healthy volunteers were initially used, there being cases in which the researcher experimented on his own person. Ramon y Cajal self-injected cholera vibrion, while Reed and Mellanby turned to volunteers for research on yellow fever and scabies (Astărăstoaie & Trif, 1998, 86).

As mentioned above, we could not yet speak of a unitary methodology, systematized in terms of approving new therapies as a result of the results obtained from controlled studies, often appealing to the prestige of medical personalities. Thus, by 1937, if a certain doctor recognized for his activity, working within a prestigious medical institution,

applied a certain treatment to his patients, and another famous doctor, from another institution, also recognized, applied another treatment for the same condition, the results were compared, communicated and the drug that obtained the best score was required. There was nothing organized, nothing conclusive.

New frontiers

The discovery of antibiotics as a means of combating infectious diseases has revolutionized medicine, while being a prime example of the role of integrating laboratory research and the need for a systematized and controlled approach to clinical research. Thus, in 1928 Alexander Fleming accidentally identified a substance with bactericidal properties, produced by bluish green mold, and only in 1945, following the publication of the results of the first clinical trials on antibiotics by Howard Florey and Ernst Chain, penicillin was approved and subsequently used in the treatment of infections.

The clinical trial for the approval of streptomycin, conducted between 1946 and 1948, was considered the first randomized trial (Doll, 1998,1662-1882). Tuberculosis has been known since antiquity and, over the centuries, millions of people have fallen victim to it, from all social backgrounds, from anonymous to literary characters or celebrities of the artistic world.

At the end of the nineteenth century, German microbiologist Robert Koch identified the pathogen in the form of a rod-like bacterium, a bacterium that is known as "Koch bacillus", and at the beginning of the twentieth century, the French Calmette and Guerin developed the tuberculosis vaccine, called BCG, after the two researchers. However, despite these advances, tuberculosis continued to claim victims and the time had come to discover its cure. Not long ago, streptomycin was discovered, an antibiotic that had proven effective in the treatment of infections, and will also be tested against tuberculosis. The trial was conducted under the aegis of a prestigious scientific forum in Great Britain, namely the "Medical Research Council", with the participation of six centers, being led by two outstanding personalities of the British medical community, Philip d'Arcy Hart, pioneer of randomized clinical trials and Sir Austin Bradford Hill. The latter had tuberculosis in his youth and, although he was cured, his ability to withstand physical exertion was impaired, which prevented him from having a very active life. For this reason, he was forced to opt for office work, less physically demanding and took a job at the Medical Research Council, then at the London School of Hygiene and Tropical Medicine. He introduced randomization into clinical trials while insisting on the importance of

medical statistics. He was concerned with identifying an algorithm for stratifying subjects to find the criterion that would distinguish responsive patients from non-responsive patients.

Regarding obtaining informed consent, Bradford Hill was of the opinion that two types of consent should be operated, namely one type for current medical practice and another type for research. In the meantime, these issues have been clarified and made operational.

Competing with the streptomycin trial for primacy is the trial investigating the effectiveness of whooping cough immunization. This trial started before the other, but results were not reported until 1951. In fact, this aspect matters less, what matters is that medical science had managed to provide conclusive evidence following trials conducted according to a modern methodology and respecting ethical norms, as they were formulated at the time. The year 1946 records a new premiere, this time in oncology, with the introduction of chemotherapy, a weapon that will dominate oncological therapies for more than half a century, the result of research work carried out by American researchers Alfred G. Gilman and Louis S. Goodman. Despite the great achievements in the field of medical science, achievements that contributed massively to the evolution of medicine towards what it is today, the twentieth century, as we will tell below, was deeply troubled by the most serious violations of human rights in the entire history of medicine and medical research, bringing immense damage to the image of medicine and doctors, compromising the very notions of doctor, medicine and research.

Genocide in the name of science

Totalitarian regimes, whether extreme right or left, are known for their profoundly inhumane character. More often than not, these regimes have caused the destruction of their own nations, provoked military conflicts, sowing suffering, misery and death for millions of people (Popper, 1993, 13-15). The end of the Second World War, in 1945, revealed to all mankind the darkest face of the Nazi regime, by discovering the horrors committed in the extermination camps of Auschwitz, Birkenau, Mathausen, Dachau, Ravensbruck, despite the fact that even at that time there were legal regulations on medical research involving human subjects, regulations that provided for the obtaining of informed consent, protection of minors, etc. (Hostiuc, 2022). Not surprisingly, this topic is treated with the utmost attention, as the scale of the phenomenon has triggered the process of redefining medical ethics and establishing legally binding rules governing the field of clinical research.

The Nuremberg Trials opened the series of acts of justice by which the most heinous criminals of the twentieth century were tried and convicted. It is no surprise to anyone that the regime that preached "a religion of hatred" had succeeded in perverting the minds and moral consciences of otherwise intelligent people who put their medical knowledge at the service of absolute evil, people whose judgment had been perverted by the ideas of the regime's "philosophers." Thus, Rosenberg, in *his Mythus,* emphatically stated that "it (the National Socialist conception) does not accept .... neither Christian love, nor Freemason humanism, nor Roman philosophy" and considered democracy and love of neighbor a sign of weakness, a "feigned decay of values", as Martin Bormann believed that "National Socialist doctrine is not compatible with Christian doctrine".

The most sinister figure remains for history that of Joseph Mengele, the one nicknamed "the angel of death" (Roland, 2022, 94-100). He graduated from the Faculty of Philosophy and then from the Faculty of Medicine, later becoming a prominent member of the National Socialist Party. Being wounded on the front in the USSR, he was repatriated and, after recovery, was sent as a doctor to Auschwitz, where, in this capacity, he zealously applied the directives of the party whose policy was aimed at exterminating individuals belonging to the "inferior races" (Gavrilovici, 2007, 169).

Reading about the activity of this veritable monster, one can see that the notions of doctor, researcher and medical research have been seriously compromised, diverted from their natural meaning. Preoccupied with genetics, obsessed with the idea of imposing the superiority of the Aryan race, of blue-eyed blondes at the expense of other races and ethnicities, Mengele systematically acted to annihilate, to exterminate those declared "inferior" while obtaining German super-soldiers, capable of resisting in extreme conditions. In order to achieve these goals, he abused in the most reprehensible way the life, physical integrity and dignity of human beings unable to defend themselves or express their will, calling his acts of gratuitous cruelty "scientific experiments". To this monster fell victim one thousand five hundred pairs of twins, mainly gypsies, of which only two hundred individuals survived.

For example, let us list some of these "experiments": injection of blue dye into the eye, injections of chloroform into the heart, intravenous injections of gasoline, unnecessary amputations without the most basic rules of asepsis, without anesthesia, intentional infection with agents of typhus and tuberculosis, while at Dachau, a thousand prisoners were infected with malaria. We can also list other such acts of cruelty, such as: the sterilization of Jewish women with X-rays performed at Buchenwald, the infliction of

wounds by mustard gas (at Oranienburg), and not to forget the experiments on children, especially twins. And in other camps there was torture of prisoners in the name of science, such as inflicting phosphorus burns, blood transfusions from a typhus patient to a healthy individual, cooling the body by immersion in water to -2.5 degrees Celsius, shooting with poisoned bullets and the string can go on, the list has not been exhausted. Most of the victims of these cruelties died in terrible torment, and their bodies were sent to prestigious German universities for study.

Convicted in absentia of crimes against humanity, Dr. Mengele skilfully escaped sentence and emigrated to Latin America, where, passing from one country to another, he lived to be sixty-seven, never showing any remorse for his horrible deeds by which, together with the other executioners, they sought to turn concentration camps into huge laboratories for experiments on men.

Of the same ideological and political extremist origin as Nazi Germany, Japan's ruling class in the first half of the last century pushed the country into a devastating war aimed at asserting the supremacy of the Japanese Empire in the Asia-Pacific area. Against the background of this racist ideology and by abusing in the most despicable way the inability to defend themselves of the Allied prisoners of war as well as of the civilian population in Japanese-occupied Chinese territory, they committed atrocities almost impossible to imagine by a human being endowed with reason, feeling and a shred of moral conscience. After the Japanese occupation of China in 1936, a special unit (actually an extermination camp) was established in Harbin and officially named "Gendarmerie Political Department and Research Laboratory for Epidemic Prevention", Unit 731 for short, under the leadership of Shiro Ishi.

Originally known as sawmills by locals, the entire complex was dedicated to research into the production of chemical and biological weapons and, at the same time, the extermination of an impressive number, in the tens of thousands, of ethnic Chinese, Mongolians and Allied prisoners of war. As in Europe controlled by Nazi Germany, horrors were committed "in the name of science" and called "experiments". These included vivisections without anesthesia, exposure to extreme temperatures, organ removals, amputations, deliberate infection with pathogens to study the course of the disease, some prisoners were drowned or buried alive. The list goes on, adding contamination of the drinking water network with chemicals or bombs containing cholera, typhoid or plague pathogens to the camp and adding to the list of victims the Chinese civilian population in the region.

In fact, Unit 731 "prevented" the spread of infectious diseases by cultivating pathogens on intermediate hosts, the settlement having real flea and rat breeders. The lives of neither children nor pregnant women were spared, all in the name of science, in fact the desecration of science in gross violation of the most basic moral principles.

As in the case of Germany, the "religions of love", a term used with contempt by the Nazis in reference especially to Christianity, were replaced by the religion of hatred. Taking an example from their German colleagues, Japanese doctors also collaborated with various Japanese universities, sending the mutilated bodies of their victims to study. After the Battle of the Midway Archipelago, the Pacific War took another turn, and in early September 1945, Japan surrendered, which was the final act of World War II.

In releasing the prisoners from the camps, the Allied troops inevitably discovered Unit 731, despite Japanese attempts to destroy evidence and the fact that Shiro Ishii had ordered his subordinates, before abandoning the camp, to carry the secret with them to the grave, being prepared, in good Japanese tradition, to commit suicide if they were captured and interrogated. In the case of these war criminals, guilty of crimes against humanity, justice can be said to have achieved them to too little extent. Most of Shiro Ishii's collaborators worked for Japanese pharmaceutical companies after the war and became prosperous businessmen.

As for Shiro Ishii, he acquired immunity from General Douglas McArthur, on condition of disclosure of the results of experiments at Unit 731. Thus, one of the most sadistic war criminals, with tens, perhaps hundreds of thousands of victims on his conscience if we refer to the Chinese population affected by the contamination of the drinking water network, escaped unpunished. He emigrated to the U.S., where he participated in research in the development of biological weapons, capitalizing on the victor's advantage and for his own benefit the odious experience gained in the sinister extermination camp that was Unit 731.

"Ethics is not for geniuses"

Under this title will be presented for analysis and reflection some cases that provoked, at that time, disapproval and concern from the public opinion due to the way in which certain clinical trials were initiated and conducted by prestigious personalities or respected institutions, but who put different interests above the good of patients, considering, at the same time, that hierarchical position and professional training give them the right to rank above ethical standards of good medical practice. These cases have remained in the history of medicine and medical research as deviations from

moral conduct and, once revealed, the scientific community has made serious efforts to avoid the recurrence of similar situations in the future. The defenders of those involved could have argued, for example, that the experimental projects presented a low degree of risk and that they did not reach the gravity of those during World War II. However, at least the attitude of superiority and contempt towards some human beings seen as worthless objects has led to unequivocal condemnation of unethical conduct in initiating and conducting those clinical trials. If public opinion has been reported on high-impact cases, it is appropriate to mention some smaller projects, if for no other reason, at least as a belated tribute to the victims. Thus, in 1906, Dr. Richard Strong of Harvard University infected twenty-four Filipino prisoners with the pathogens of cholera and typhoid fever without their consent. In 1908, a number of orphaned children were inoculated with tuberculin by researchers in Philadelphia, the children being referred to as "used material", and in 1927, Vollmer attempted to demonstrate the effectiveness of a rickets medication by keeping a number of children in the dark to demonstrate that the proposed drug could substitute for natural sun exposure (Hostiuc, 2022). Even in the years after World War II, certain unethical practices were not completely renounced, an enlightening example in this regard being the administration of radioactive iodine to a number of pregnant women who later aborted, and the embryos were studied in the laboratories of the University of Iowa, the horrible experiment being initiated and led by the United States Atomic Energy Commission.

Holmesburg case

These are several experiments that took place between 1951 and 1974 on Holmesburg prison inmates in the United States of America, conducted by dermatologist Albert M. Kligman and under the aegis of the University of Pennsylvania, experiments that aroused many controversies about their character, controversy arising from the revelations in Allen Hornblum's book, published in 1998 as "Acres of skin: Human experimentation at Holmesburg Prison". The author gathered information by interviewing prisoners and former prisoners who told him that, in exchange for participating in Dr. Kligman's research, they were rewarded with sums of money, but that they were not asked for written consent, as required by the procedures in force. Also, Hornblum's investigation demonstrated the questionable scientific character of the experiments, even sometimes dangerous, for example treating certain skin conditions with X-rays or applying to the skin dioxin, a toxic compound, the dermatologist

being paid by "Dow Chemical" to test the effects of dioxin in contact with the skin. Also, in this context, the use of drugs with psychotropic effect on detainees was revealed (Gavrilovici, p. 170).

As for Dr. Kligman's attitude, it seems that he saw in prisoners only "acres of skin" and, defining himself as a genius, used to say that ethics is not for geniuses, considering that a personality, a leading representative of the profession, possessor of superior intelligence is not obliged to conform to the rules that ordinary people must follow without deviation, and that there are human beings who, Because of their disadvantageous situation, they can be treated without respecting their most basic rights (Astărăstoaie & Trif, 1998, 68).

Jewish Hospital case

Another case of deviation from ethical conduct regarding clinical research is that of The Jewish Chronic Disease Hospital in New York, where, starting with 1954, an experiment consisting of subcutaneous injection of live tumor cells was carried out in elderly, non-oncological patients, but suffering from other chronic conditions, with the stated purpose of testing antitumor immunity in these patients. Going beyond the fact that this experiment had no scientific value and did not bring any benefit to patients, the worst thing is that they were not asked to agree to participate in such a project.

The medical institution was brought to justice and an extensive investigation was launched around this matter. Thus, while three of the doctors, who have since resigned, admitted that the patients had not been informed of the contents of the injection administered, others argued that the information had only been verbal, while others argued in their defence that, since it was something 'harmless', information was not necessary. The subject was debated in the American press, in the New York Times, on 21/01/1964 appearing the article *Hospital accused on cancer study. Live cells given to patients without their consent.*

Willowbrook case

It is an experiment conducted over a fourteen-year period beginning in 1956 at the Willobrook Institute in New York, which is actually a school for children with severe mental retardation (Gavrilovici, 2007, p. 171). Due to the poor hygiene conditions in this settlement, many of the children fell ill with viral hepatitis with virus A, this disease being practically endemic, which was a justification in the context of the events. The admission of children to the institute was conditional on the parents' acceptance that their son or

daughter be included in the study that was being conducted, which consisted of intentionally inoculating healthy children with hepatitis virus for the stated purpose of stimulating antibody production.

The non-therapeutic character, the absence of any useful information for the development of medical science, as well as the constraints to which these children and their families were subjected are all reasons to declare the experiment as a deviation from ethical conduct in research (Goldby et al., 1971), of gross violation of human rights, being nothing but another abuse in the name of science.

The Tuskegee case

Conducted over the course of no less than forty years, respectively between 1932 and 1972, this case became an emblem, a reference point for unethical behavior in medical research on human subjects, also bringing into discussion the racial theme (Gavrilovici, 2007, pp. 167-168). It is a project coordinated by the National Institute of Health in the U.S., a study that included four hundred members of the African American community in the state of Alabama, most of them of at least modest if not poor economic condition, sick with syphilis. Since enrollment, investigators have acted incorrectly, as participants were not informed what disease they were suffering from, being told they had "bad blood." The study followed the natural course of the disease in these subjects, although syphilis had been known since antiquity, so no new scientific information was brought. The enrolled subjects benefited only from periodic check-ups at which their travel expenses were reimbursed and their meals were provided, and at death their funerals were organized.

The most serious aspect, from an ethical point of view, is that the study continued in the same non-therapeutic manner after 1945, the year when penicillin, the first antibiotic entered the therapeutic arsenal, proved effective in the treatment of syphilis. It can also be discussed the unfair manner in which these people belonging to a disadvantaged category by economic status and subjected to racial discrimination were approached and enlisted (Astărăstoaie & Trif, 1998, 67). In 1997, on May 16, President Bill Clinton gave a speech to the eight survivors of the experiment that awakened public opinion in the United States about the slippages that had overshadowed, over the years, the hard and honest work of so many professionals devoted to their craft and people.

Conclusions

At a brief evaluation, some substantial deviations from the etics conduct stand out, which we find in all the cases presented above. Among these, we note the discriminatory attitude and abuse of authority by investigators in relation to subjects, the absence of usefulness of experiments and last but not least, in fact the most serious aspect reported would be the violation of human rights and placing financial interests above the interests of participants.

George Santayana, one of the great philosophers of the twentieth century, said in *The Life of Reason* that those who do not remember the past are condemned to repeat it, a warning that humanity, unfortunately, has ignored too many times, and the consequences have been dramatic (Santayana, 1905, 284).

But perhaps the most precious lesson of the past is precisely the errors, whether intentional or not, for which the price is huge, every effort has been made so that these errors can no longer be repeated, and medicine is forced to look to the future, in a world increasingly demanding and aware of its rights. The progress of science is necessary, but not at any cost, in any case not at the cost of subjecting human beings to unjustified risks (Sloterdijk, 2018, 55-81).

To meet these requirements, medical research is responsible for obtaining evidence of efficacy and safety for each drug entering the market, which is provided by the results of randomized, controlled clinical trials conducted internationally, involving thousands of subjects. After all, each of us wants that, when we need treatment or surgery, they help us improve our health, with disagreeable effects as bearable as possible and, in any case, that do not endanger us. From the experience of the pandemic years, let us remember that the main objection against Covid-19 vaccines was the short duration allocated to studying them and the fear that, in the long run, undesirable effects would occur that could not yet be highlighted.

In order to achieve these standards, information and communication technology, medical expertise, statistical expertise and, last but not least, national and international regulations on good medical practice that impose on all actors involved a high standard ethical and scientific conduct.

The past, with all its errors, whether intentional or not, is a closed page, but its lessons must serve the new generations of doctors and researchers, engaged in the battle for life, so that they do not deviate from the right path, the only one that leads to performance, success and maintaining the respect that practitioners of this profession enjoy from society. Perhaps it

should be said that current generations of medical researchers still face the shadows of the past, having to remove the stigma of those who have been mentioned earlier, and perhaps others, whose undignified deeds have not been revealed. Progress has been an imperative for all sciences, and medicine has been no exception, but, given the circumstances in which information and evidence are obtained, impeccable conduct is required of the researcher, in the light of the Hippocratic tradition, the general rules of conduct in human relations and the laws in force. Thus, if historical landmarks have marked moments in the continuous evolution of science and medical progress, with specific references to some ethical aspects, in the following will be a brief presentation of the main philosophical currents that provide both moral norms and criteria and perspective of an analysis of the phenomenon studied, respectively clinical research.

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