

The history of ethics in research with human subjects

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Abstract

This article contextualizes the emergence of the field of research ethics in historical, social, and political events over the last 60 years. It draws a distinction between professional ethics and bioethics, focusing on the historical and philosophical precedents of the latter field. It also presents the appearance of research ethics as a result of the disclosure of cases of scientific misconduct, discussing the first regulations on research ethics, the guidelines contained in the Belmont Report, and its influence on the creation of bioethical principlism. The article also analyzes the functioning of research ethics committees and possible limitations to scientific activity. Finally, it highlights some issues that remain unsolved, such as payment to research participants, the conduct of research on unconscious people, using children in experiments for testing new drugs or new therapeutic indications, the definition of minimum risk, and the way bioethics has been taking place in developing countries.

Keywords

history of ethics; bioethics; research ethics; professional ethics; principlism

Introduction

The importance of a historical review lies more in the development of concepts than in the chronology of events. For a concept that is evolving as fast as that of ethics in research with human subjects, changes happen in a fluid way and do not allow the establishment of clearly delimited time periods. In relation to this topic, it is not possible to speak of progress, since there is not a path laid out towards a goal. Some initial ethical achievements, such as the respect for people or the proposal for sanitary

justice, have been slowly modified. This is an observation of fundamental importance to the Southern Hemisphere, where injustices and inequalities are endemic and progressively severe. The bioethics made in Latin America has to fight, from its own trenches, for the rescue of those who do not have power and for the protection of impoverished populations (Kottow 2006).

Alaistar MacIntyre (1984) observes that social practices produce quantifiable and negotiable external goods and internal goods that are related to excellence and the ethics of performance. Research ethics, strictly speaking

the researcher's, is a professional ethics that distinguishes correct and incorrect actions, generally based on an explicit code. The fundamental aspects refer to the probity of not adulterating the different research steps, not manipulating the results or their publication, respecting the participation and priorities of peers, not plagiarizing, dealing with money honestly and transparently, and not taking ownership of material or intellectual goods. All these aspects refer to the integrity of scientific work and the reliability of the external goods produced, differing only in specific details from the enforced moral demands in other professions. Transgressions of the professional code are analyzed by peers and, occasionally, by institutional superiors, being evaluated in the bioethics' antechamber.

Bioethics presupposes that professional behavior is under control, and prefers to be concerned with the relationships established between the professional and the individuals or communities in which welfare and scientific practices are applied. In the case of research on human subjects, the emphasis will be on the effects that the project designed by the investigator will have on the participants. The primary function of research ethics is to protect the participant, an individual that voluntarily submits himself to a risk, frequently experiencing conditions of vulnerability either for social reasons – poverty, malnutrition, lack of power – or for having a disease that may or may not be the motive for his recruitment into the study. The scientific probity demanded by professional ethics is subordinate to the transparency and sustainability of the researcher-participant relationship provided by bioethics. Item 5 of the introduction of the Declaration Helsinki (2000) points out that the well-being of research participants must prevail over the interests of science and society, that is, the internal goods protected by bioethics will have priority over the external goods contemplated by professional ethics.

The distinction between professional ethics and research ethics is especially relevant because of the controversies raised nowadays amongst researchers willing to increase the risks assumed by participants for purely scientific reasons – the use of placebos or sub-medications, for example – and research ethics, which protects the research subjects and raises doubts about the strict value of so much scientific rigor. The controversy gains new strength from the discrepancies between the medicine based on evidences and the ethical reticences or triggered practices. Nevertheless, there are hybrid situations in which the transgressions of professional ethics are of interest to bioethics because they produce damage to the participants or the society, as when researchers omit reporting harmful effects of the drugs studied.

A paradigmatic case is that of researcher Nancy Olivieri, who revealed negative data about the drug deferiprone, which she herself was studying, contradicting the interests and the instructions of the sponsoring lab and of her own university. Her ethical integrity was questioned by researchers who had no scruples about committing transgressions, thus doing immoral and inappropriate science. The conflict has been summarized as

the contrast between the values of science and the values of business; however, when the integrity of scientists fail, there is a conspiracy between science and business that turns against bioethics, the protector of patients and participants (Schafer 2004, 2007).

This article contextualizes the emergence of the field of research ethics in historical, social, and political events over the last 60 years. It draws a distinction between professional ethics and bioethics, focusing on the historical and philosophical precedents of the latter field. It also presents the appearance of research ethics as a result of the disclosure of cases of scientific misconduct, discussing the first regulations on research ethics, the guidelines contained in the Belmont Report, and its influence on the creation of bioethical principlism. The article also analyzes the functioning of research ethics committees and possible limitations to scientific activity. Finally, it highlights some issues that remain unsolved, such as payment to research participants, the conduct of research on unconscious people, using children in experiments for testing new drugs or new therapeutic indications, the definition of minimum risk, and the way bioethics has been taking place in developing countries.

Historical precedents

Modern science, which began with Galileo's experiments (1564-1642) and the enthusiastic approval of Francis Bacon (1561-1626), maintained, for a long time, the certainty of being an objective activity that was both beneficial to humanity – to the degree that it promoted knowledge – and ethically neutral – to the degree that only moral values related to a correct practice should matter. Mistakenly, Max Weber (1864-1920) is cited in order to support this thesis of science's moral neutrality, but what he actually defended was that science receives from society the responsibility of solving certain problems, being its results applied according to priorities that are also social. These two social moments — that which appeals to science and that which uses its results — are subordinated to reflections on values and are, therefore, eminently ethical. Weber insisted that it was necessary to separate the scientific method itself from all subjective influence in order to conduct research in a morally neutral way, without biases or distortions.

Throughout the 20th century, techno-scientific development reached such proportions that the scientific method could not be applied without weighing the benefit-risk relationship. This gained special importance in biomedical research in which the study of living beings could cause irreversible damage or even death. Resistant to ethical evaluation, contemporary scientists still oppose the introduction of a research ethics that is committed to establishing moral rules especially related to protecting people and communities involved in scientific studies. History recognizes, however, that long time ago the ethical reflection about studies on cadavers or living beings, both human and non-human, was already present.

André Vesalio (1514-1564) broke the theological and moral taboo of studying human anatomy through

cadavers to refute the teachings of Galeno (129-199), who believed that the dissection of pigs and monkeys would provide reliable information about the internal morphology of the human being. Anatomic dissection of a human cadaver was only officially authorized in 1537, by Clement VII, since doing it before that was considered sacrilege, unless it was a man and, possibly, a criminal. The value and the certainty of knowledge resided in theological study, and not in natural observation, which was less revered. With the apex of experimental research on non-human animals since the 17th century – with Harvey, Hales, and Hooke –, a more systematical ethical reflection also arose, under the form of a controversy between the vivisectionists and the ones who opposed this practice. This controversy intensified until the 19th century, when the first Societies for the Protection of Animals were created, at the same time when the scientific community defended experimenting with non-human living beings, with the support of figures like Virchow and Bérnard.

A characteristic phenomenon of this period was self-experimentation: Sertürner studies the effects of morphine on himself, Hunter self-inoculates material extracted from a luetic chancre, Davy inhales nitrous oxide to know its properties, Auzias vaccinates himself with small doses of syphilitic material, and picturesque Brown-Séguard mentions in his lectures that at the age of 72 he was able to rejuvenate with self-administrations of testicular extract from guinea-pigs and dogs. There were plenty of critics arguing that putting the researcher himself at risk was as unacceptable as hurting other people.

The first glimpses of patient participation in their own clinical decisions occurred in 1914, when it was considered illicit and punishable to invade a person's body surgically without her previous consent. This doctrine only found legal strength in 1957, when the expression "informed consent" was introduced for clinical situations, which had already occurred ten years earlier in research involving human subjects. Studies with humans were practiced with growing assiduity, but the researchers did not feel compelled to carry out an ethical reflection specific to their activity.

Pierre-Charles Bongrand presented an extended list of biomedical experiments and self-experiments on humans in his doctoral thesis (1905), coming to the conclusion that, for the sake of science, these studies, even though "immoral", were "occasionally necessary". Under controlled conditions, it was justifiable to submit the "idiots", the terminally ill, prisoners and those sentenced to death, but not the vulnerable people, such as the poor, children, or pregnant women, to the risks of research. Mentioning voluntary consent and the need for compensation, Bongrand recognized a state of "placid ignorance" in society that needed to be changed (Amiel et al. 2001). He pronounced an enthusiastic compliment to intra-hospital research, in which a sick person should not be seen as a lab animal yet was not considered to be so isolated in her "human glory" as to be exempt from

participating in studies that would bring health to herself as well as to countless other human beings.

Philosophical precedents

Research with human subjects as an established procedure is very recent, and one can even affirm that, until the end of the first third of the 20th century, there were no reasons considered urgent enough for dedicating moral reflection to such an incipient practice. Modernity has continued exacerbating its trust in rationality and in scientific positivism, celebrated initially by Francis Bacon and more recently by Spengler and Hottos. Ethics in scientific research is better nurtured by the skeptics, who see a source of risks in techno-scientific progress for human beings' adaptation to their natural and social environment, as well as for the survival of humanity.

The most well-known critic of techno-scientific expansion was Hans Jonas, preceded by the writings of Günther Anders, which present a vision that is purely pessimistic and lacks ethical propositions, pointing to an insurmountable gap between the Promethean achievements of instrumental expansion and the emotive poverty of facing it with imagination, anticipation, regret, and responsibility. As the process accelerates, the human being becomes a producing agent, with the consequent atrophy of the ethical dimension that could judge and occasionally limit its pragmatic enthusiasm (Anders 2002). Hans Jonas (1984) prefers to change his critique into an ethical appeal to scientists' responsibility in re-dimensioning their activity and not expanding it to zones of risks that are unknown and threatening for future generations. Jürgen Habermas (2001), who had developed the idea of an instrumental reason that confuses means and ends, imerged in an overpowering pragmatism that colonizes communicative reason, has very recently taken his concepts to a critical analysis of genetics and its risks for the human essence.

None of these philosophical approaches to the hegemony of biotechnoscience have had a direct impact on ethics in scientific research, but they have served to show that science is not absolutely immune to ethical or social relevance considerations. As biomedicine comes closer to knowing and modifying human biology, it gains importance, as does the anthropological reflection found behind Habermas' text and in writings of Ronald Dworkin (2000).

The dawn of research ethics

What has been said so far does not contradict with the visible and explicit emergence of an ethical concern with research involving human subjects since the Nuremberg trials. On this occasion, World War II criminals were judged, including some doctors that had led or participated in torture disguised as research. Hans-Martin Sass (1983) presents situations that took place even prior to the war, as that of a circular produced by the German Ministry of Health in 1931, a document that regulated, in a very avid and contemporary manner, "new therapies and human experimentation", addressing the

will of the participant, the difference between therapeutic and non-therapeutic trials, and the responsibility of the doctor as a researcher and as a therapist. The cultural and legal oblivion in which this regulation of the Third Reich fell into contrasts grievously with another publication of that time, which successfully introduced the concept of “lives unworthy of being lived”, and became the basis of genocide, the concentration camps, and the medical torture that characterized that period (Binding et al. 1920).

The publication that had the greatest impact in the period immediately after the war was a book written by Alexander Mitscherlich and Fred Mielke (1978). The book documents and comments on the Nuremberg trials, to which doctors were submitted for having sacrificed human lives to study the limits of tolerance to extreme conditions, such as hypothermia, oxygen deficit, and massive injections of pathogenic germs. In a statement whose force resides precisely in its tautology, Andrew Conway Ivy denominated the criminal experiments as crimes. As a specialist participating in the trials of the Nazi doctors, Ivy (1977) let himself get involved in a discussion in which medical crimes were tentatively justified, if not pardoned, as manifestations of an exceptional ethics that was in force in times of war. This interference of ethical arguments in situations of criminality and genocide would collect its pernicious dividends in 20th century principles, when bioethical analyses proliferated in favor of medical participation in military affairs and torture (Kottow 2006).

From the horrors revealed in these trials was born the Nuremberg Code, which also represents a historical rupture. Although this document has been triggered by such revelations, it does not refer to them, but to the conduct a scientific researcher should follow. It is a demonstration of wisdom that this first research ethics code has avoided referring to highly anomalous situations and has preferred to concentrate on general ethical norms that are valid for all research. Even so, the fact that a trial of war criminals has inspired a research ethics code is still worthy of attention.

Putting aside the habitual evaluation of Nuremberg, but without denying its importance as a foundation for all subsequent reflection on research ethics, some important perceptions on this respect deserve to be mentioned. The people that drew up the Nuremberg Code, as was the case with American Ivy, who coordinated the process, were imbued with a high esteem for individual autonomy. For this reason, they emphasized the free will to participate in experiments, without being able to admit that the fundamental ethical failure of the medical barbarities was not the absence of consent, but the incomprehensible destruction of another human being.

It is noteworthy that the ten points of the code take special care to protect participants, justify the social relevance of studies, and conduct them with idoneity. The first paragraph refers to “voluntary consent”, taking almost as much space as all of the other paragraphs combined. It wasn't enough to ratify the free will of

participating from that moment on; there had to be a guarantee that a society would not go back to losing moral orientation to the point of becoming corrupt and committing the evil acts of national-socialism. Research ethics is not sufficiently present just because of a robust informed consent; it is necessary, besides this, to assure that society is respectful of human rights (BURT, 1996). According to this analysis, the implicit conclusion from Nuremberg is that individual freedom has to take place in an environment of trust in social institutions, including the scientific world.

Alexander Mitscherlich always spoke of medicine without humanity, of cruelty, or of cultural rupture, but not of scientific research. This is also the understanding of the Nuremberg Tribunal, which issued death sentences and extended prison sentences, which correspond to serious offenses but not to scientific immoralities. The distinction is fundamental, since occasionally one appeals to the excuse that the negligences detected by ethics in biomedical research are insignificant in comparison to what happened in Germany, an invalid excuse for contrasting incomparable categories – one from the area of flagrant human rights violations, and the other related to scientific activities.

Misconduct in scientific ethics

Scientists are mistaken when they state that the ethical control of research is not necessary since immoralities would only have happened in anomalous social situations, as in the national-socialist dictatorship in Germany (1933-1945). This opinion is easily refutable when one remembers that the scientific infamy of Tuskegee Valley started in 1932, and only after the beginning of the second half of the 20th century did they begin to systematically detect the ethical transgressions to which scientific activity is susceptible, supported by the normative vacuum that existed during the 20 years that separated Nuremberg from Helsinki.

The end of World War II also marked the beginning of the Cold War and the threat that was felt to be very real of an imminent third world conflagration. As a result, a special emphasis was put on studying the so-called ABC weapons – atomic, biological and chemical – and their effects on human beings. The ethical control of these studies was discussed in the government and military levels; in some cases, the Nuremberg Code was adopted, and in others the liberty of bending the norms and delineating them *ad hoc* for each project was preferred (Moreno 1996). Forty years later, ambiguity persists to the point that an Advisory Committee on Human Radiation Experiments summoned in 1964 detected ethical flaws in transparency, protection, and compensation for the participants of numerous studies conducted by or for governmental institutions (Faden 1996).

Less known in biomedical literature is the debate raised around the experiment designed by psychologist Stanley Milgram in order to study obedience, which was presented to the volunteers as a research about “studying and learning”. The participants stayed in a booth where

they controlled a console of switches that supposedly activated electric currents of 15 to 450 volts that were to be applied on a person sitting in an armchair separated from the participant by a transparent wall. The participant had to formulate verbal association questions and punish incorrect responses with electric shocks that, as the researcher enticed, became stronger and stronger each time. The subject on the chair contorted with every shock and became inert with the more powerful ones, without the participant knowing that there was actually no electricity and that the reactions were simulated. The experiment finished if the participant refused to raise the intensity of the shocks or if he applied the more intense ones, which were supposedly lethal. Milgram (1963) observed that 60% of the participants had obeyed the researcher's instructions and applied the supposedly lethal doses of electricity, a finding that was considered very significant in psychological literature.

Criticism became more severe immediately after the Behavioral Study of Obedience was published, primarily complaining that the participants had been recruited under trickery and without a correct procedure for informed consent, which is not rare in social sciences, in which one searches for the spontaneous and innocent reaction of the participant.¹ Secondly, it was considered that the subjects had been harmed psychologically by recognizing that their will could be followed to the point of seriously harming or even killing a person in obedience to peremptory solicitations. This case leaves a variety of teachings, the main one being the fact that social sciences are not free from the ethical demands that are recognized in the biomedical disciplines. Any intervention that involves human beings or that can affect them must be analyzed and accompanied by an ethics committee, since a study or the disclosure of stored data are potentially harmful. It is necessary, therefore, to recognize the possibility of damage that is not organic or empirically measurable.

Thirdly, even if the current ethical code has not been explicitly violated, the study hurt the ethical sensibilities of many professionals who felt that the respect owed to the research subjects had been violated. And finally, the intentional misleading, even if it was necessary because of the study's design, could not be justified if it implied possible harm to the participant. Misleading a competent person is equal to recruiting people with reduced discernment without permission, for in both cases one acts in the absence of the informed will of the subject. However, the classical defense of consequentialism was not lacking, recognizing that misleading is reprehensible only if it causes significant damage, which was not the case here. The accomplishments of Milgram himself were not lacking either, arguing that his participants had not suffered any harm (Herrera 2001).

Additional ethical aspects are present in another classic example of immoral research, which was detected many years after its beginning. With the sponsorship of the United States Public Health Service, in 1932, a study began on the natural course of syphilis in an African-American population in Tuskegee, which at that time

seemed plausible because there was not a treatment that favorably modified this natural course. However, when in the 1940s evidence was obtained about the therapeutic value of penicillin, a cheap and easily accessible antibiotic, it was obvious that clinical ethics should override research methodology and provide a treatment capable of curing syphilis and reducing its complications and lethality. Nevertheless, the protocol was not modified, nor was the study interrupted before 1972. In other words, this experiment was conducted for 40 years and served as a basis for many scientific publications of great impact. The study was only interrupted because of joint efforts from the Public Health Service employees themselves, the media, and public opinion (Caplan 1992).

The case of Tuskegee suffered generalized repudiation, but also had defenders, who wielded the "fallacy of presentism" to complain that one should not measure the past with present criteria (Benedek & Erlen 1999). It was not licit, according to these defenders, to criticize the lack of informed consent, since this doctrine did not exist in 1932. Finally, it was affirmed that a large number of the participants received treatment that was not in the study's protocol, which refutes the acuity of the project and invalidates its results due to method deviations. The lack of justification about the risks that the population recruited for the study had to undergo still had to be verified. The commonly used argument that offering placebos to poor populations does not mean denying them treatment, since they never had it, is not sustained in the Tuskegee case, where it is considered ethically imperative that penicillin had been introduced as soon as it was available. Therefore, the excuse that it would be coherent to not give what had not existed until then is not considered acceptable. This is a notorious example of inconsistency in ethical thought: that which is accepted in Thailand is not permitted in Tuskegee.

The indisputably immoral experiments of inoculating mentally retarded children boarding the Willowbrook State School with the hepatitis virus (Krugman et al. 1967) and of injecting cancerous cells in seriously ill patients being treated in the Jewish Chronic Disease Hospital in Brooklyn received special attention (Langer 1966). In these studies, multiple ethical transgressions took place: mentally vulnerable people, who were in a dependent situation – confined subjects –, were recruited, and serious harm was intentionally caused to them.

In this period, Henry Beecher's article (1966) and Pappworth's book (1967) were published, both of which alarmingly detected the great rise in clinical trials on human beings, the expansion of budgets, and the competitiveness of scientists. These findings made the authors fear that ethical inaccuracies would become more frequent and more serious at a time when there were few attempts to regulate research on human beings. After presenting 22 reports of publications related to clinical trials marked by severe ethical deficiencies, some of them cited in this article, Beecher curiously finishes with some general recommendations, such as strengthening informed consent, considering benefits

and risks, and rejecting publication in cases of severe transgressions; however, the author abstains from opining on the convenience of formal normative instruments or from commenting on the Declaration of Helsinki, promulgated not long before.

What happened in Germany, as well as the psychological experiments conducted by Milgram in 1966 and, especially, the widely debated Tuskegee case, opened the discussion about the legitimacy of using scientific data obtained through ethically questionable trials. Susan Reverby (2001) redeems the experiment by gathering multiple artistic, documental, academic, and political forms in which the Tuskegee episode proves fruitful in inspiring fictitious reports with ideological objectives. It has been said, mistakenly, that the participants were deliberately infected by the researchers, that many received treatment with penicillin for intervening diseases because they moved out of the study area, and that the racial focus of the research would be a typical case of discrimination. The ethical analysis should make a careful abstraction of these additional controversies, since they did not put the immorality of the study into perspective, just as the Holocaust could not be justified by saying that it did not only affect the Jews and that the alleged numbers are exaggerated.

According to some authors, the immorality of experiments proscribes using its findings, under the penalty of making researchers think that the ends justify the means. According to others, the results of immoral trials should be ignored to show ethical indignation and to discourage such practices. It is argued that an ethically deficient job does not have scientific value, but it has also been suggested that these cases be published with an ethical comment. The pragmatic perspective sees the use of the information obtained as a recognition that the sacrifice of the participants was not totally in vain, while the ethical perspective sanctions these experiments to discourage them in the future and because, in addition to its immorality, they lend themselves to evasions and distortions (Moe 1984).

From time to time the attempt to rescue scientific findings obtained in ethically contestable conditions emerges, arguing that science should not be judged by its immorality, but only to commiserate with it, because, if there is no harm, there is no immorality (Proctor 2000). The 1975 Declaration of Helsinki suggested that research that violated ethical norms was not to be published. The conflict still has not found an adequate solution, since biomedical research with severe ethical failures that are diversely evaluated continue to appear. An example of this is the forced resignation of Marcia Angell, editor of the *New England Journal of Medicine*, for having questioned and rejected ethically questionable manuscripts.

The first research ethics guidelines

With the notable increase in scientific activity, especially in the field of biomedicine, it soon became evident that ethical regulations more complete than the one offered by the Nuremberg Code needed to be

drawn up. Nuremberg as well as Helsinki were understood as ethical, yet legalistic documents. The Declaration of Helsinki was considered more useful and more extensive, mainly because of its concern regarding both participants' informed consent – or the informed consent of the legal guardians, when the person is considered incapacitated – and the distinction between therapeutic and non-therapeutic trials.

The Nuremberg Code was known as a reactive and accusative document, whose prospective effect was very tenuous, which explains the immediate creation of study groups inside the World Medical Association (WMA). The groups presented, in rapid succession, a Resolution on Human Experimentation, in 1953, a Guide for Researchers, in 1955, and an Ethical Code for Researchers. Exploring the literature, a 1962 rough draft of the Declaration of Helsinki prescribed the inclusion, as participants, of prisoners of war, civilians detained during military occupations, incarcerated individuals, and individuals who are mentally incapable of giving their own valid informed consent.

The deliberations of the WMA culminated in 1964 with the Declaration of Helsinki, inaugurating the academic analysis, later assumed by bioethics, of the probity of biomedical studies. Since the beginning, the declaration has been confronted by the scientists' skepticism of the rigorous regulations that produce serious limitations on the freedom of researchers and do not permit them to even reflect on the possibility of doing away with the patient's informed consent or conducting studies with children or mentally incapacitated adults — all situations which the WMA proposed not to authorize.

The opposition to the Nuremberg Code, which preceded the Declaration of Helsinki, came from Hill (1963), one of the most reputed statisticians at the time, who was skeptical of the idea that the different types of clinical research could be regulated by the same code. His proposals maintain the spirit of the code, but avoid the normative application, preferring a situational decision, and recommending the use of informed consent only if the two groups in the controlled trial are unequal in relation to risks and benefits, and the use of placebos only if there is no useful treatment with which to compare the new active agent. Hill insists that ethical obligations always come before experimental obligations, a premise that would nowadays be expressed by affirming that clinical ethics has to take precedence over research ethics.

At the same time the Declaration of Helsinki was promulgated, the UK Medical Research Council published a document that emphatically affirmed that the study of a new medical procedure should be compared with the best method in current use, which would waive the need to use placebos, unless there was not an existing effective therapy yet. Informed consent, especially in non-therapeutic trials, should emanate from an interpersonal relationship supported, but not substituted, by a signed document. When people lack the ability to give their consent, they should not be recruited for non-therapeutic studies that imply some kind of risk. The

content of the British document is very similar to that of the Declaration of Helsinki, both of which are very clear in considering the protection of individuals prior to the interests of science or society, and are situated as defenders of those unable to exercise their own will. By reinforcing the fundamental character of informed consent, the revision of the Declaration of Helsinki in 1975 instituted the need to create research ethics committees and advised not to publish works arising from studies that contain possible ethical objections.

The Nuremberg Code's emphasis on voluntary consent is taken up in the Declaration of Helsinki, with the more refined language of informed consent. In relation to the protection of participants, especially when they lack the mental competence necessary to be able to consent in an informed way, the Declaration of Helsinki recommends that clinical trials make a clear distinction between therapeutic studies (which intend to develop some type of therapeutic improvement for the patients involved) and non-therapeutic studies (whose objectives have nothing to do with the medical condition of the selected participants). It is understandable that the risks participants might run while in therapeutic studies are more acceptable, since there is an expectation that they will receive direct benefits. Consequently, when it is impossible to obtain informed consent, it can be inferred that that participant can not be recruited for non-therapeutic studies that would not benefit him, but would make him run unnecessary risks.

The Belmont Report and bioethical principlism

Rarely has the significance of the Belmont Report (1978) been cited as a turning point in research ethics, yet it was certainly the most relevant milestone in the field during the 1970s. The document established a clear distinction between the trajectory followed by research ethics in the United States and its evolution in the rest of the world, a distinction which eventually became an issue of frank debate after the Declaration of Helsinki, revised in 2000.

The Belmont Report is the result of the deliberations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978) and of the National Bioethics Advisory Commission (NBAC), established in 1995 and 1996 with the aim of revising, ratifying, and unifying previous efforts in the field. These are two of the various *ad hoc* committees that the US Executive created to study problems and propose lines of action in a specific social area. The Belmont Report intentionally introduces the language of ethical principles when it demands that every study be respectful with people, beneficial for society, and fair in its balance between risks and benefits. Since the beginning, however, the absence of a fourth principle to incorporate a community dimension is lamented, thus unleashing a two-faced debate that still persists (Childress 2000).

The Belmont Report was a fertile area for dominant principlist bioethics in a large part of the Western

world, so it is not a coincidence that the debate about research ethics has followed the features of Georgetown University's four principles, in a rhetorical expansion that has produced many variations and not merely a few controversies. There was a series of national committees that took the responsibility for specific bioethics topics upon themselves and established some general lines of reflection for research ethics, including the incorporation of public opinion, and the development, structuring, and control of institutional review boards, which have served as a model for research ethics committees in other countries. A permanent concern has been the recruitment of participants with so-called "decisional incapacity", that is, with reduced mental capacity, which impedes them from fully participating in the process of informed consent.

It is possibly in the confrontation between the interests of science and human values that one can best perceive the change research ethics has suffered since the middle of the 20th century. This change began with Leon Kass' criticism (1990) on the excess of ethical theory and the insufficient respect for the Declaration of Helsinki in relation to informed consent; additionally, Jay Katz (1993) formulated the idea in 1972 that one should observe a especially careful respect for autonomy when one solicits informed consent for studies that will not be beneficial for the participant. For a long time, respect for autonomy was sufficiently robust to demand that whatever detrition was begun in the name of community interests be clearly justified (Childress 1990); however, a subtle distinction of codifying principles according to an order of priority and presentation was made, conceding the first place to autonomy (Childress 2000). According to Katz, research protocols should follow a series of conditions – such as assessing possible risks and weighing them against possible benefits, as well as respecting fairness in the selection of participants – before being submitted to consideration on the informed consent of the subjects whose participation was sought. In a certain manner, autonomy was already protected by these previous conditions.

Like wizards' apprentices, their defenders saw the desire for autonomy grow to the point of forgetting John Stuart Mill's questioning, that is, that liberty should only be limited when it interferes with the liberty of others, a necessary condition for equanimous coexistence. A retrocession in the unrestricted celebration of autonomy was necessary, beginning with a demand for its limitation in favor of a social ethics engaged in one just order (Veatch 1984; Callahan 1984). During the years in which Henry Beecher criticized the moral quality of many studies, Kass (1990) and Katz (1993), both of whom agreed on the importance of autonomy, discussed the best way to defend it: while the former emphasized scientists' moral maturing to go beyond the excess of bioethical theory, the latter replied that theoretical reflection is essential and should bring about a clear distinction between medical practice and biomedical research, also affirming that only exceptionally and justifiably should biomedical research demand that individuals participate in trials whose objectives do not correspond to their interests.

Sensitive to criticism, principlist bioethics itself began to wear down the initially sacrosanct principle of autonomy, above all in relation to special clinical situations, to subjects who are mentally impaired, and, particularly, in the world of the research participants (Kottow 2004). To bring about the weakening of autonomy, it was necessary to undertake a theoretical work aimed at invalidating the difference between therapeutic and non-therapeutic trials and insisting on the distinction between research ethics and clinical ethics in order to abandon the commitments with the participant as patient, submitting him to the therapeutic orphanage so as to better deplete the pharmacodynamics of the study. Besides this, the concept of benefits was blurred in order to create fictitious scientific objectives and values that were easier for rhetorical management, such as “the advancement of knowledge”, “social good”, or “benefits for future generations”.

The controversies that preceded the most recent Declaration of Helsinki (Edimburgo, 2000) marked the beginning of deep discrepancies between interests created, on the one hand, and defenders of a research ethics rigorously committed to the unrestricted protection of the rights of patients, participants, vulnerable individuals, and defenseless communities, on the other. The disagreements sank deeper and tended to favor the more powerful in such a way that an asymmetric convergence was created in which the position of researchers and sponsors predominates over the protection of people.

The declarations of the World Medical Association are the most well-known norms, but are not the only ones that try to regulate scientific activity, especially in the biomedical arena; there are also the regulations of the Council for International Organizations of Medical Sciences (CIOMS/WHO) and of the Nuffield Council on Bioethics, the documents of the European Council and several declarations related to specific topics, such as research on embryos or on genetic material and epidemiological studies. In general terms, they exhibit large overlaps in the intention to protect patients, participants, and communities, but with a tendency that became more and more notorious for respecting the interests of researchers and sponsors, and for succumbing to the desire to commercialize knowledge, procedures, and products, in conformity with the 90:10 polarization of research – 90% of the resources are destined to the study of only 10% of the diseases that affect wealthy societies. In Latin America, the most used referential continues to be the Declaration of Helsinki, since it is still committed to protecting patients and participants and still has a format that is easy to consult.

Research ethics committees

Both the Declaration of Helsinki (1975) and the Belmont Report (1978) insisted on the need to create instances directly related to scientific activities. Such instances would adapt the purposeful, but scarcely binding, language of the declaratory documents in order to regulate all of the bioethical aspects of research on

living beings, especially on humans. Citing very briefly, the research ethics committees developed the following characteristics:

- they differ from hospital ethics committees in their composition, functions, and norms;
- they are not composed of natural scientists only, including representatives from the social disciplines and from the community;
- the participation of other professionals or members of the community is not ruled by a principle of representativity, but of idoneity;
- following the model of the institutional review boards, local ethics committees are preferable because they know their own institution and researchers and can more easily summon them to be able to go forward with the study;
- research ethics committees are doubly obligatory: every study should be revised by them, and every researcher should abide by the ethical corrections that the committee demands;
- the deliberation of the research ethics committee not only guarantees conformity with the general norms, but also analyzes each protocol individually;
- the research ethics committees assure informed consent, the proportionality of risks, the details of the scientific method that could imply risks, the economic aspects that watch over probity, and the pertinent use of the results;
- the research ethics committees should work in a regulated and documented way to found their deliberations as well as to create jurisprudence.

The profusion of scientific studies in the field of biomedicine has greatly intensified the amount of work for the research ethics committees, making them release their reports in a routine and hurried manner. Faced with this crisis, different countries are creating instances for controlling the committees' work and saving them from analyzing critical projects, as with studies on genetics, ethnicity, and those on the forefront of biotechnoscience and nanotechnology. A pioneering example of this is the Brazilian National Commission on Research Ethics (Comissão Nacional de Ética em Pesquisa – Conep – in Portuguese). A similar initiative had been suggested by Katz (1993), in the sense of putting a preliminary national committee before the research ethics committees, since the author suspected that the committees would feel more obliged to protect the interests of their institution than the research subjects.

Limitations to scientific activity

Throughout time, scientific activity insisted on its innocence and good will, which made every moral interference or restriction to its liberty superfluous. This immunity became difficult to sustain to the extent that scientists participate in military projects, invade critical frontiers of knowledge, such as genetics and nanotechnology, or choose areas and research topics because

they are economically promising. The official responses in different nations has been to cede to pressures from civil society and provide ethical control by prohibiting or withholding public financing for studies on non-human animals, for the use of embryonic cells, for reproductive cloning, or for other morally critical areas.

An initiative for self-regulation was put in place after the Asilomar Conference in 1975, in which a group of prominent scientists concluded that the risks of certain studies on recombinant DNA called for a moratorium that suspended some experiments but allowed others that could proceed under strictly cautionary measures. The moratorium was neither long nor absolute, and there was no rigorous control in respecting it, but it seems to have shown that researchers are disposed to regulate their activities for ethical reasons, even though others have come to the opposing conclusion that science would not be able to moderate its own activity. Nowadays, there is a moratorium on research on reproductive cloning, but it is obvious to everyone that the oversight of this prohibition is impossible, even when supported by restrictive legislation.

Pending topics

The procedure for obtaining informed consent has been transformed, changing from a process of joint deliberation between researcher and participant to the signing of a document that hardly summarizes or substitutes what should have been a form of personal communication. Research ethics committees commit the mistake of analyzing this document, on many occasions prepared as a generic form, as if it were a faithful testimony of the information provided. The successive revisions of the Declaration of Helsinki sharply wore down informed consent, especially in the case of people who could not exercise it fully.

After the 50 year anniversary of the Nuremberg Code promulgation, the Physicians for the Prevention of Nuclear War presented the Nuremberg Code of 1997, ratifying individual autonomy and informed consent, and at the same time criticizing the downplay and degradation of this principle since the 1947 code. Biomedical research should always be destined towards concrete people, and the protection of human rights, as well as of the principle of informed consent, should not cede under the supposed higher interests, even if this holds the study back. The quality of the defense of human rights and autonomy are measured by the deal that is given to individuals who are unable to consent, those who should be protected from every study that only benefits others (Wunder 2000).

The position of the 1997 Nuremberg Code is presented as a criticism in an area that is notoriously more propitious for facilitating the work of researchers, at the cost of reducing the participants' protection. The Council of Europe proclaimed the Convention on Human Rights and Biomedicine (1977), whose essential traits establish that: research on human beings should only occur when it can not be replaced by another method to obtain the

desired knowledge, the risks be reasonable, there is a scientific as well as an ethical evaluation and approval, and, above all, that one looks for a consent that is free, clear, specific, and documented. Experimentation with individuals who are incapable of giving their voluntary consent is severely limited, but not proscribed, and there are escape clauses that permit incorporating them even though the trial is not for their direct benefit (Manuel 2000). The convention is not binding, and the European countries adhere partially or totally to its articles or develop norms about aspects that were not included in it, which in France, for example, was interpreted as the freedom to research, susceptible to strict conditions, above all in relation to the participants whose consent is impossible to obtain or considered fragile (Amiel et al. 2001).

The most recent milestone in research ethics was the promulgation of the Universal Declaration on Bioethics and Human Rights (2005). The declaration has incited diverse reactions, from being celebrated as a document that indicates new courses for ethics to generating very negative opinions about the confusion of concepts and the banality of asseverations that it contains. When it comes to research ethics, one has to recognize that the declaration seems precipitated for a discipline that is not sufficiently solidified, since it was not able to elaborate the topics beyond their presentation in the Declaration of Helsinki (2000). At the most, it ratifies, with a flaccid language and the predominant use of the conditional tense, that the interests of the communities, as well as of the vulnerable and mentally incapacitated, "should" be considered.

There was a dilution of the original sense of biomedical research, oriented to obtain real therapeutic benefits, not simply marginal modifications of what already exists. The protocols flatter themselves, nowadays, for denying every intention of benefit to the participants and protect themselves with empty formulae, such as social good, future benefits and increase of knowledge, behind which academic or economic interests deprived from any social horizon hide. With the same argument of the supposed general benefit, the barrier that exempted vulnerable people from being recruited, unless it was for their direct benefit and with acceptably limited risks, is broken. Now, it is argued that these populations should be included so that their pathology is not excluded from being investigated, thus bypassing the ethical norms that only permit the recruitment of vulnerable people when the study has clear therapeutic intentions for them.

A similar confusion happens with the controversy about emergency treatment on unconscious subjects who don't have a responsible person present, between experimental treatments (when it is the only one that exists) and research in critical clinical situations (when alternatives are compared). It has been defended the idea of accepting the researchers' criteria so as to make the decision to initiate an experimental study in these situations (Truog 1999). In favor of the protection owed to the subjects, the study should only be accepted if it

complies with three conditions: a) there is no reasonable access to the decision of a responsible person and there is no known previous expression of a position by the patient; b) the existing treatment has serious flaws in effectiveness and/or complications; c) the experimental treatment has reasonable and well-grounded expectations of improving the prognostic.

Research ethics should face a topic that has been shyly avoided so far, under the conception that science and economy do not mix, an idea that has already become completely obsolete. The contemporaneous motor of scientific activity includes profit, conquering market niches, competitiveness, and acquiring patents. Curiosity has been replaced by pragmatism, in a climate in which researchers, sponsors and scientific institutions care for their respective interests, at the same time in which they promote the recruitment of altruistic participants who assume risks but do not receive any benefits from their participation. Illustrating this confusion of interests, the biological initiative of the Human Genome Project was born under the guard of the US Department of Energy, which is responsible for US nuclear programs.

Any payment exceeding the minimum is considered undue incentive; however, participants are unknowingly a means for others to obtain benefits that are not criticized as being disproportionate. This scorn for the participants becomes perverse when one proposes to make participating in studies a civic duty that every citizen must comply with for the sake of public good (Rhodes 2005). From the US President's Commission comes the suggestion, initially thought for children but soon after widened to include adults, to use a "slippery slope of risks/benefits": the more risks or benefits for the people, the more demanding the level of competence required to accept or refuse the study; and, on the contrary, if the intervention has fewer consequences, decisions would be accepted beginning at lower levels of discernment. Even though it has its level of logic, the rule is unnerving, since it impedes people from making decisions that are more important for themselves.

The described rule casts its shadow on a relationship between risks and incentives that has been the source of controversy. Those who are against incentives argue that it would be totally inadequate to offer important incentives to encourage possible participants to sign up for high risk studies. Nonetheless, the undue aspect of incentives is not in accepting them, but in offering them in exchange for assuming risks that, without the incentives, would be unacceptable. Such risks must be repulsed as being disproportionate, with or without incentives.

Another rhetorical strategy that aims at facilitating researchers' abilities to include participants lacking in discernment to opine is the definition of minimum risk, which, by its insignificance, could be imposed on subjects who lack free will (Wendler 2005). One definition of minimum risk equates it to the daily risks; another one thinks of it as equivalent to the medical routine to which the patient is submitted. Both are *ad hoc* definitions hardly accepted by a kind of bioethics concerned

about supporting vulnerable subjects, as Latin American bioethics should be (Kottow 2005).

The bioethics of developing countries

In relation to bioethics in the Southern Hemisphere, one can say that biomedical research is being diverted to developing countries for pragmatic reasons, contemplating disproportionately greater benefits for the sponsoring nations than for the host countries. At the same time, a defensive rhetoric to minimize the accusations of exploitation has been developed (Hawkins & Emanuel 2005). The most influential side of the academic bioethical reasoning and of the creation of international regulations tends to make the protection of participants and patients relative, with statements whose imprecise language hides an actual tolerance to the preferences of the greater interests.

This tendency is clearly seen in the controversy that generated the most recent Declaration of Helsinki, which is illustrated by the addendums included by researchers who were more interested in science and in the publications that such addendums guaranteed than in the research subjects. The objective of these reviews is to defend the use of placebos, deny the guarantee of post-trial benefits, and justify the lack of commitment to the needs of communities that host these studies.

The bioethics of developing countries needs a robust direction that recognizes, defines, and clearly indicates the malpractices and transgressions of research ethics, such as exploitation, coercion, manipulation of informed consent, the weakening of commitments with offering benefits, the therapeutic orphanage of using patients as participants, and the use of vulnerable people in non-therapeutic research whose intent is to serve commercial interests. Vulnerability, exploitation, coercion, and manipulation are all topics that have been the protagonists in fierce controversies and deserve to be studied in detail.

This topic goes beyond the confines of this article, but it is important to call attention to a rhetoric strategy that defines these diverse authoritarian impositions in such an exact manner that a large part of the current practices can be morally exempted. This same discharge ability practiced by bioethics in developed countries needs to be analyzed under the perspective of those who are affected, for a careful and sensitive look detects that one exploits and coerces in a subtle way, which hides the damages produced. The liberal use of vulnerability, which is a concept that denotes fragility, but not damage, when one is dealing with vulnerable individuals and populations hides the lack of concern with the weakening of the host countries where research is carried out without offering the necessary care in the majority of cases (Kottow 2003).

The international research ethics guidelines presented in this article should provide a basis for the action not only of researchers, but also of research sponsors and organizers. This is a way of assuring the dignity of the participants and of getting human rights closer to science. The steps for scientific research include moral

coherence on the part of the investigation team, and demand detailed reviews on the part of the regulatory agencies in each country. The advance of science has brought about important outcomes for the well-being of people; however, these gains in quality of life can not be reached at the cost of the dignity of research participants and of the integrity of the scientific community.

Note

1. T.N.: The term *informed consent*, used in international research ethics documents and in the description of studies done in the international context, corresponds to the expression *consentimento livre e esclarecido* in Brazilian regulation.

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