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EDITORIAL

Clinical Research and Internal Medicine: between Science and Bioethics

Ricerca clinica e medicina interna: tra scienza e bioetica

The internist is probably one of the specialists with more inclinations towards clinical research, and in particular research aimed at testing drugs. Since King Attalus III of the Kingdom of Pergamon (138 BC-133 BC), who experimented poisons and antidotes on criminals condemned to death, the idea of testing medications in human subjects has always been present. Between the end of the 19th and the beginning of the 20th century for the enthusiasm in achieving scientific progress, trials in human subjects were imposed without major ethical concerns, thus leading to the enrolment of vulnerable patients, such as psychiatric and institutionalized patients and prisoners, generating unjustifiable abuses.

The Nuremberg trial (1945-1946) marked a decisive step for medical research involving human subjects. For many years the Nuremberg Code (1947) remained in oblivion, the proof being the scanty relevance it had in the most important medical journals. Nowadays the Nuremberg Code is considered the most important document in the history of ethics in medical research, since it stated the existence of universal and inviolable human rights. It was used as a base to the Declaration of Helsinki and successive amendments (the last one in Seoul, in 2008), and also to other important modern ethics documents such as the CIOMS (*Council of the International Organizations of the Medical Sciences*) Procedure (1982), the *International Conference of Harmonization for the Good Medical Practices* (1997), the approval of the universal Declaration on the human genome and the human rights during the XXIX Assembly of the UNESCO (1997).

In 1964 the *World Medical Association* developed the Declaration of Helsinki, primarily addressed to physicians, as a statement of ethical principles for medical research involving human subjects. This led to further attention towards ethical issues in clinical research, in a period still characterized by studies carried out without respecting the most basic ethical procedures. As an example, in the Tuskegee Syphilis Study, the natural history of the syphilis was evaluated in 412 patients of black race and poor condition in

Alabama, and 285 of them died during the four decades of observation. The US Senate condemned the fact, determined the indemnification of the survivors, but did not sanction the researchers responsible for the study.

The experimental design of clinical studies may be a further issue from an ethical viewpoint. In 1931, before the drugs against tuberculosis were developed, gold treatment (sanocrysin) was compared with the administration of water in the treatment of patients with tuberculosis, and since then clinical protocols with placebo have been controversial. Up to 2000, when a strong debate raised due to a trial performed in patients with AIDS and living in Africa, by comparing zydodthymidine and placebo at a time when therapeutic options of proven efficacy were already available. Placebo has been crucial for the development of clinical research, since it constitutes a fundamental step in the application of the experimental method, allowing statistical efficiency as well as clarity in the interpretation of the results. However, the use of placebo is justified only under a strict ethical evaluation, when effective treatments do not exist, the risks for patients are very low and they will not suffer a severe damage during the observation period.

From the discovery of the penicillin, probably the most important event in the history of therapeutics of the 20th century, the development of drugs has been of great transcendence. Today we can add molecular biology, genetics and a future scenario with medication *à la carte*, but there is no doubt that to pursue this progress it is essential to operate inside a frame of ethical legitimacy. From the Declaration of Helsinki in 1964 up to its last amendment, several approaches and concepts have changed. Many procedures have addressed the risk of irregularities and frauds, from the patients' recruitment (i.e. deception, compensation, etc.), to the informed consent (i.e. scanty information, fraudulent practices), from the need of transparent relationships between the sponsors and investigators, to the control of all the phases of study and drug development, up to the marketing

and advertising. As a scientific and ethical issue, by starting a new clinical study, investigators accept to publish the results, including negative ones, and the registration of studies in public databases is now requested by the editors of the most important medical journals as a condition for publication. Last but not least, an important fact has been the appearance of the multidisciplinary independent committees, whose role is to control the fulfilment of regulations and protection of the rights of the enrolled subjects. The participation of the subject to the clinical research must be voluntary, free, and duly informed (as per the informed consent).

The internist who assumes the role of investigator must have a solid scientific preparation, including at least basic

knowledge of methodology for research. Respect of the regulations and good disposition to accept monitoring, audits and regulatory inspections, are necessary to assure the quality of research. Finally, when feasible, to establish a good doctor-patient relation is of great value to guarantee an aware participation and to optimize patient's adherence to the study procedures.

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