Pierre Baumann and François Ferrero: An official inquiry of the clinical research activities (1946-1972) of Roland Kuhn (1912-2005)

Thomas A. Ban's comment

An Overview of the History of Drug Regulation and Ethical Conduct in Clinical Research*

To provide some orientation points in history to the Kuhn inquiry in the following an overview of the history of drug regulation and ethical conduct in clinical research in the United States is presented.

Regulation

One of the essential prerequisites for neuropsychopharmacological research is the availability of psychotropic drugs with known therapeutic effects. During the 1950s several drugs were introduced by the pharmaceutical industry for the treatment of schizophrenia, depression, mania and anxiety disorders. Yet, it was not before the 1960s that approval of drugs for specific indications in clinical use, based on demonstrated efficacy, became a requirement in the United States.

The first Pure Food and Drug Act in the United States was introduced in 1906 (Barkan 1906) but until the early '60s all regulations were related to safety requirements and to the separation of prescription drugs from over the counter medications. The scope of legislation was extended in 1962 with the enactment of the Kefauver-Harris Amendment (KHA)[1] (Barkan 1985) which stipulated that: the effectiveness as well as the safety of a new drug has to be established before the drug is released for clinical use (Kravitz 1966).

[1] In addition to safety and efficacy, the KHA also stipulates that (1) drugs have to be produced in accordance with sound manufacturing practices; (2) the distribution and the use of investigational drugs have to be adequately controlled; (3) prescription drug labelling and advertising have to confirm to governmental approval; and (4) provision has to be made by the manufacturer (distributor) for keeping records and reporting on the distribution and feedback of approved drugs, so that an ineffective or unsafe drug could be removed from the market, or its directions for use revised.

Extension of the legislation from proof of safety to efficacy has had a major impact on clinical research with psychotropic drugs. It has also led to the implementation of structured clinical drug development in three successive phases. Phase I, "human pharmacology," starts when the new drug is first given to man, usually to normal subjects. Its purpose is the determination of the drug's preferred route of administration and safe dose range. Phase II, "clinical pharmacology," includes the initial clinical trials for the treatment of a specific disease or prophylactic purposes. Phase III, "clinical investigation," provides information on the efficacy, safety, optimum dose range and schedule of administration of the drug.

The single, most important influence on pharmacotherapy is the regulation that defines the requirements for approval of a new drug on prescription. To meet requirements of the US Food and Drug Administration (FDA) a drug must show a statistically significant difference (superiority) to placebo in two pivotal double-blind, randomized clinical trials which are of adequate sample size and statistical power. Furthermore, to meet the requirement that an ineffective or unsafe drug could be removed, the three-phase clinical development was supplemented with drug surveillance (Phase IV).

A resolution of the National Advisory Health Council in 1965 led to the establishment of Institutional Review Boards (IRBs). It also helped build the clinical framework in which research with psychotropic drugs operates. IRBs are to approve proposed research. Their primary objective is to ensure the safety of experimental subjects (ES) involved in the research. In 1966 the Surgeon General of the United States issued a policy statement in which various methods were listed to safeguard humans involved in National Institutes of Health (NIH) or more generally Public Health Service (PHS) supported research. Special policies were formulated for controlled experiments.

In 1966 the FDA amended its regulation with a statement of policy formulated by Terry Goddard. The "Goddard Amendment" stipulated that whenever an investigational drug is used in human beings the investigators should obtain informed consent from the ES (Goddard 1966). At the time the Goddard Amendment was introduced it served exclusively the protection of patients but by the 1980s it became a protective shield (from litigation) for studying new drugs developed by drug companies. The amendment has had an impact on breaking the old paternalistic style of doctor–patient relationship. It also opened the path for "medical ethics" to play a steadily increasing role in medical universities.

Ethics

Human experiments have been instrumental in the development of medical skills. Yet, until the mid-20th century human experiments were not controlled by legislation but by the informal code of approval of the scientific fraternity. In the middle of the19th century, Claude Bernard, in his *Introduction to the Study of Experimental Medicine,* asserted that "it is the duty and the right of the physician to perform an experiment on man whenever it can save his life, cure him, or gain him some personal benefits." But Bernard also insisted on "never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science" (Bernard 1965). The first systematic presentation of the ethics on experimentation in humans was drawn up by the Nuremberg Military Tribunal after World War II and published in 1947 in the Nuremberg Code, a legal document. The gist of the "laws" incorporated in this document are: (1) the ES must give voluntary (informed) consent prior to being included in an experiment; (2) the experiment should yield fruitful results for the good of society and its results should not be attainable by any other means; (3) the experiment must be based on prior animal studies and knowledge of the natural history of the disease; (4) the degree of risk involved in the experiment should not exceed the potential benefits of the research for society; and (5) the ES should be at liberty to bring the experiment to an end (Nuremberg Military Tribunals 1947).

The principles of the Nuremberg Code were revived in 1955 by the United Nations Third Committee on Social, Humanitarian and Cultural Questions and incorporated in 1964 in the Helsinki Declaration (HD), based on the Declaration of Geneva of the World Medical Association and the International Code of Ethics. The Helsinki Declaration emphasizes that the "responsibility for clinical research always remains with the research worker" and "it never falls on the (experimental) subject" (Williams 2008). The Declaration has been endorsed by several nations and numerous medical associations; the Judicial Council of the American Medical Association recommended its adoption in 1966 at its annual convention.

During the second half of the 20th century clinical studies with psychotropic drugs have become a large component of research in which human subjects are involved. To meet fully the obligations of ethical conduct, the "fruitful results for the good of society" must be *disseminated and integrated* with the existing body of knowledge. Within our societal structure, it is the task of

marketing to disseminate the findings in clinical research and it is the responsibly of education to integrate the new information with existing knowledge.

*Adopted from Thomas A. Ban: Preface. In: Salzman C, editor. Diverse Topics. In: Ban TA, series editor. An Oral History of Neuropsychopharmacology The First Fifty Years Peer Interviews. Brentwood: American College of Neuropsychopharmacology; 2011, pp. ix -xxx.

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April 9, 2020