Ethical issues on experiments *in anima nobile* on hepatitis

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Introduction

Scientific debate on hepatitis at the beginning of the 20th century focused mainly on the aetiology of the "icterus catharralis"[1]. After the 2nd World War discussion centered on a probable infectious agent. Since the 1960s, after the identification by Baruch Blumberg of the Australia antigen[2], other agents of viral hepatitis (VH) have been identified. Transaminases and hepatic biopsy in the 1950s, and serological diagnosis, gave additional visibility to the VH and contributed to the growing efforts on research of passive and active immunization of the 1970/1980s. From 1990 on, the hepatitis C pandemic helped to focus scientific and economic interests in the production of drugs. Research methods and goals changed but phase three experiments – clinical trials – still require interventions in people.

The history of diseases provides many examples of research in human beings, volunteers or not. In the case of hepatitis, resistance of the scientific community to accept its infective etiology[1], in part due to the difficulty of developing an experimental animal model[3], may have stimulated even more experiments in human populations. While the aetiology of hepatitis was being discussed, leptospirosis and yellow fever – diseases whose predominant clinical presentation (icterus and fever) include them in the same key for differential diagnosis – already had clearly defined aetiology, animal models for research, and diagnostic tests[4]. Although recognized as "campaign jaundice"[5] since 1915, it was only during World War II, when 200.000 American soldiers and five million German militaries and civilians were struck by it, that emerged "a great impetus to the understanding and prevention of the disease"[6].

In the 1960s, human blood, feces, and secretions from the sick were inoculated in volunteers to try to understand transmission and propose prevention of the hepatitis. Nowadays, experiments *in anima nobile* require compliance to ethical requirements and the informed consent is *sine qua non* to their implement[7].

We discuss contradictory aspects of the informed consent in classical human experiments on hepatitis in the first half of the 20th century in view of the design of clinical trials today.

We bring to discussion particular aspects of the experiments *in anima nobile* on hepatitis through a selection of classic studies pointing to contradictory ethical aspects including the informed consent. Many authors have shown the advances in legislation on ethical issues concerning research in human subjects[8,9]. Research on AIDS has been, on the last two decades, at the center of debates that emphasize the concepts of vulnerability and difference or diversity as attributes of social groups and individuals, that should be of special concern as ethical issues of research protocols[10]. Studies on hepatitis seem to point to similar issues although they were not frequently the object of debate in the old days. These questions are discussed considering sociocultural and time diversities, focusing the multiple dimensions that derive from technology and scientific uncertainties.

The informed consent

Although the informed consent, included in the CNS Resolution 196/1996 as free and informed consent, is relatively new[7], recognition of its relevance was presented at the turn of the 20th century[11]. The Parliament of Prussia in 1898 asked for government action, motivated by controversies concerning the research on syphilis prevention that required inoculation of serum from patients in prostitutes, who became ill. The Rudolf Virchow's report concluded that no physician was allowed to inject infective serum in a volunteer without previous consent[11].

Krugman and Giles[12], authors of the studies on hepatitis at Willowbrook State School (WSS) between 1956 and 1970, begin their research at the same year of the elaboration of the Project for the Code on Ethics in Experiments on Human Subjects that was presented at the General Assembly of the World Medical Association in 1961. The authors refer that the studies at WSS were in accordance with the Project that allowed research with legally incompetent subjects once the informed consent of their legal representatives was obtained[12,13]. In 1964 this Project was revised into what became known as the Declaration of Helsinki and presented a more restrictive version concerning the legally incapable although maintaining the possibility of

their participation as subjects of research[14]. Similarly, the Brazilian CNS Resolution 196/96 (item IV.3)[7] also admits research involving children and adolescents with restricted mental capabilities or mental disease and subjects with impaired capabilities to provide consent, requiring that the protocol provide clear justification for this choice of research subjects and that informed consent is provided by legal representatives, and information is provided to the subjects to the limits of their capabilities.

Vollmann and Winau[11] point out that even before the Nuremberg Code in 1947[15] – that established that only the legally capable should be able to volunteer as subjects of research experiments – regulations derived from public debate and from the Prussian Parliament in the 1900 were more restrictive and provided that "minors and incompetent subjects were generally excluded from non-therapeutic research, as they could not give valid informed consent."

Nevertheless, as pointed out by Kotow[16], it was the Belmont Report in 1978 that developed in its full complexity the principles of autonomy, beneficence, non-maleficence, justice and equity regarding the research in human subjects[17]. This report came to light six years after the closing of the hepatitis research unit at WSS in 1972[18]. Publication of the results of the WSS studies provided the ground for a broad debate on ethics in research[6,18-20], and some of the arguments for and against these protocols seem to have been recently rekindled in the debate on ethics in AIDS research protocols in Africa. Garrafa and Prado[10] show the relevance of revisiting the past as they expose the many social and economic issues that may be involved in proposals of ethical relativity.

The argument of high endemicity

Nowadays, electing volunteers for research requires a methodology that guarantees the control of selection biases and of ethical principles. The choice of sex professionals could be justified by the perspective of development of therapies and preventive measures for diseases with higher incidence/prevalence in that population. In 1970, Krugman e Giles[12] justified an experimental study that had lasted 14 years, with the argument of high endemicity of hepatitis in an institution for special children (Willowbrook State School). In 2011, the European & Developing Countries Clinical Trials Partnership (EDCTP) – non-governmental organization founded on 2003 – considering Sub-Saharan Africa as the most affected region in the world regarding these infections, impairing its development and leading to extreme poverty, took as a mission "to accelerate the development of new or improved drugs, vaccines and microbicides against HIV/AIDS, malaria and tuberculosis, with a focus on phase II and III clinical trials in Sub-Saharan Africa"[21]. HIV, malaria and tuberculosis were selected for the discussion of the argument of high endemicity because these diseases present nowadays scientific challenges and social mobilization for their control that seem similar to the situation of hepatitis when the WSS experiments were underway. What are the implications of using diverse ethical criteria in experiments *in anima nobile*? To study the progression of HIV infection can we inject live malaria parasites in HIV patients in China, even if this protocol has been rejected in the USA? Lurie and Wolfe[22] ask these questions, and answer that "these are not simply hypothetical worst-case scenarios"; this research has "already been performed".

Kotow[9], discussing the informed consent on clinical trials, presents the question of vulnerability of populations of some countries that corroborate such studies suggesting that their position as underdeveloped countries may generate almost colonial relations that may limit their capacity to adequately defend the interests of their population.

Carvalheiro[23] points out that the inclusion of developing countries in studies of HIV vaccine developments seem to be justified not only by the genetic variability of HIV but also to elude the vigilance of regulatory agencies, so often inexistent or careless of such questions in the Third World. What are the differences between the questions raised by Carvalheiro[23] and the Willowbrook study[12]? In the first case, the autonomy of the subjects can be limited by not so well understood research protocols and the unquestionable scientific authority of the principal investigators. In the second case, the autonomy of the subjects was transferred to the parents or legal guardians that were informed that the children could be benefited by immunity against the disease.

Krugman and Giles[12] took extreme care to justify the human experiment and the process of obtaining informed consent. For instance they argued that since the susceptible children would be invariably infected when interned at WSS, artificial induction of hepatitis could have a therapeutic effect. They also comment that only the children whose parents had given written informed consent were included in the study and that the technique to obtain the consent had evolved with time. With the strategy of group meetings involving families and a multidisciplinary team (social psychiatry specialist, physician, nurse and attendants) they obtained more agreements.

However, we should pose a question – to avoid anachronism in the judgment of the procedures of the past[24] – as to the possible influence of the list of renowned institutions that approved the research protocol on the agreement of the parents. How many parents of special children, for so long segregated, in the USA or anywhere, in the 1950s (or today), would be able to decide freely the consent to a study informed to be prophylactic and sanctioned by so many well-known scientific institutions?

To answer this we recall the critics of that time such as Goldby[20]. In his letter to *The Lancet*, he emphasizes that the "duty of a paediatrician in a situation such as exists at Willowbrook State School is to attempt to improve that

situation, not to turn it to his advantage for experimental purposes, however lofty the aims." The Editor seems to ratify this opinion commenting on the affirmative that the study was therapeutical: "It is hard to accept that view, even when applied to a school where a very high proportion of children will, in existing conditions, be infected anyway" [20]. These comments suggest that the institution was not considered as a model and that many parents could be leaving their children there for lack of options. It shows the possibility of a situation of extreme vulnerability of these families of children with special needs back in the 1950/1960, even in the USA.

We can imagine similar situations in populations whose only possible access to medication may be linked to the consent to participate in clinical trials. It seems to have occurred in the AIDS Clinical Trials Group Study 076 (ACTG 076) when, after years of proven efficacy and widespread use of the antiviral zidovudine for prevention of perinatal transmission of HIV in the USA, pregnant women in other countries still had no access to such medication[22].

Clinical trials and partially known results

Although Saul Krugman passed into history as a pioneer of hepatitis B vaccination[6], many of the more than 700 subjects of the Willowbrook Studies were not immunized[12]. They became chronically infected, as observed by the researchers, although they had no means at that time to further understand their findings: "The extremely long-term, if not permanent, persistence of Au/SH observed in nine of the 18 children in whom it was found suggests that it is not a very efficient antigen in terms of antibody stimulation or that the antibodies that it induces are incomplete"[25].

Observing these experiments with todays knowledge, it seems hardly justifiable to inject or ask the subjects to swallow solutions of feces from icteric patients[26]. But, in 1945 it was not possible to predict all the consequences of this procedure. Even today, possible adverse effects of new drugs are very hard to be fully predicted before they are licensed to use and we are familiar with the many instances of the need for drug recall such as pointed out in the classical study by Beecher[27]. The frequency of human experiments on hepatitis was criticized in 1952 by Fraga Filho[28] who considered that the number of human experiments on etiology of hepatitis with similar results no longer needed further trials. Tables 1 and 2, reproduced from his doctoral thesis, show the evidence for his argument. Here are registered the number of volunteers, the authors, and the period of the study.

MacCallum[29] published a similar review for serum hepatitis presenting eight experimental studies *in anima nobile*, that took place from 1944 to 1946, with the innoculation of 548 people, 184 (33,6%) of them presenting icterus. The disease followed the reception of measles convalescent serum and yellow fever vaccine that contained human serum. The author remarks that "[...] as a result of the use of blood products on a massive scale during the period 1939-1945, a sufficient number of different 'outbreaks' of homologous serum hepatitis occurred [...]" and that, as the disease "[...] could not transmitted to laboratory animals experimental studies have been carried out in man". Apparently without perception of any contradiction, he also describes methods of inactivation of the icterogenic agent and points that it is desirable to have a routine method for serum treatment that would inactivate this agent without destroying the desirable serum properties.

The perception of the uncertainty of scientific knowledge makes us aware of the need to constantly question and adequate the meanings and uses of the informed consent[30]. The fragility of the informed consent and the autonomy of volunteers and researchers themselves, stand out when we reflect about scientific research from a historical perspective.

Koch´s postulates and scientific uncertainty

In the beginning of the 20th century, biomedical research of infectious diseases causality was ruled by the Koch's postulates and it was in this scenario where most experimental studies on hepatitis were developed.

The hypothesis of an infectious nature of *icterus catharralis* presented difficulties for lack of animal models or *in vitro* data, as required by the postulates, and human experiments were done to check the hypothesis. In a 1945 article, co-written by Albert Sabin, we read: "and by using man as the experimental animal some of the properties of the agent of infectious hepatitis have been determined"[31].

Not only the difficulties of the animal model but also the search for irrefutable evidence stimulated studies on human volunteers, often disregarding the unnecessary risks the volunteers could be standing[3,4].

In 1967, Deinhardt et al. registered that marmosets were susceptible to human hepatitis and could be appropriate animal models. But, avoiding criticism, the authors emphasized that although they had demonstrated the transmission of human hepatitis to those primates through the elevation of transaminases and compatible liver lesions they could not confirm it through the elevation of antibodies. That ratified the need for caution in the interpretation of the results and justified further human experiments: "It is yet to be proved that the agent inducing hepatitis in marmosets is indeed the agent of human viral hepatitis by the reintroduction of the agent after several marmoset passages into man"[32].

Koch's postulates are insufficient for the standards of today. As was seen later, the non-reproduction of hepatitis in experiments with animals[32] was overcome by electron microscopes and molecular biology that made possible the identification of HAV and HCV.

Table 1 – Experiments on transmission of infectious hepatitis to volunteers

Material	Author	Year	Disease stage	Route of administration	Nr. of volunteers	Positive results		Incubation (days)
						Jaundice	Without jaundice	
Duodenal liquid Feces	Voegt (467)	1942	Preicteric	Oral	4	2	2	28
	Mac Callum and Bradley (280)	1944	Icteric and preicteric	Nasopharynx	26	3	–	27-31
	Havens (181)	1944-46	Icteric	Oral	12	9	–	15-27
	Havens (185)	1946	Incubation (-15 days)	Oral	3	–	–	–
	Havens (185)	1946	Convalescence (+25 to 31 days)	Oral	10	–	–	–
	Neefe et al. (334)	1944-46	Icteric	Oral	49	28	2	17-32
	Neefe et al. (334)	1944-46	Icteric	Parenteral	3	–	–	–
	Neefe et al. (335)	1945	21 days posticteric	Oral	7	–	–	–
	Neefe et al. (335)	1947	+92 to +342 days	Oral	5	–	3	18-20
	Findlay and Wilcox (123)	1945	Icteric	Oral	73	7	10	17-48
	Paul et al. (357)	1945	Icteric	Oral	3	2	–	20-25
Serum	Voegt (467)	1942	Preicteric	Parenteral	4	–	2	19 (?)
	Cameron (46)	1943	Icteric	Parenteral	7	6	–	30
	Mac Cullum and Bradley (280)	1944	Icteric	Parenteral	6	3	–	64-92
	Havens (181)	1944-46	Icteric	Parenteral	17	8	–	20-31
	Havens (181)	1944-46	Icteric	Oral	8	7	–	21-34
	Havens (185)	1946	Convalescence (+25 to +31 days)	(?)	10	–	–	–
	Oliphant (348)	1944	Icteric	Parenteral	21	4	–	85-106
	Francis (143)	1946	Preicteric	Parenteral	8	4	–	42-47
	Oram (353)	1945	Multiple stages	Parenteral	9	–	–	–
	Neefe et al. (334)	1944-46	Icteric	Parenteral	9	1	1	30
	Neefe et al. (334)	1944-46	Icteric	Oral	3	2	–	26-33
	Neefe et al. (333)	1947	Chronic (106 to 367 days)	Oral	5	–	–	–
	Paul et al. (357)	1945	Preicteric	Parenteral	11	6	–	22-34
	Paul et al. (357)	1945	Icteric	Oral	5	4	–	22-34
Nasopharyngeal wash	Mac Cullum and Bradley (280)	1944	Icteric	Nasopharynx	16	–	2	24-28
	Neefe (334)	1945	Multiple stages	Nasopharynx	8	–	–	–
	Havens (181)	1946	Icteric	Nasopharynx	3	–	–	–
Urine	Voegt (467)	1942	Preicteric	Oral	1	–	(?)	–
	Mac Cullum and Bradley (280)	1944	Icteric	Nasopharynx and oral	19	–	–	–
	Findlay and Wilcox (123)	1945	Icteric	Oral	26	5	2	17-22
	Neefe and Stokes (332)	1945	Multiple stages	Oral	7	–	–	–
	Havens (181)	1946	Icteric	Oral	3	–	–	–

Table 2 – Experiments on transmission of serum hepatitis to volunteers

Material	Author	Year	Disease stage	Route of administration	Nr. of volunteers	Positive results		Incubation (days)
						Jaundice	Without jaundice	
Feces	Neefe (335)	1945	Preicteric to icteric	Oral and intragastric	19	–	–	–
	Mac Callum (281)	1945	Icteric	Oral	15	–	–	–
	Havens (186)	1946	Icteric	Oral	6	–	–	–
	Findlay et al. (122)	1944	Icteric	Oral	2	–	–	–
Serum	Oliphant et al. (346)	1943	Icteric	Parenteral	196	37	–	28-160
	Oliphant et al. (346)	1943	Icteric	Intranasal	3	–	–	–
	Oliphant et al. (346)	1943	Convalescence (+75 days)	Parenteral	15	–	–	–
	Mac Cullum and Bauer (282)	1944	Icteric	Parenteral	16	6	–	50-127
	Mac Cullum and Bauer (282)	1944	Icteric	Intranasal	10	1	–	80
	Mac Cullum and Bauer (282)	1944	66 to 141 posticteric	Parenteral	10	–	–	–
	Havens (186)	1944-46	Incubation (-16 days)	Parenteral	4	1	–	–
	Havens (181, 186)	1944-46	Icteric	Parenteral	13	7	–	56-71
	Havens (186)	1944-46	Convalescence (+28 to 32 days)	Parenteral	5	–	–	–
	Havens (181, 186)	1944-46	Icteric	Oral and intranasal	13	–	–	–
	Neefe et al. (334)	1946	Icteric	Parenteral	25	14	4	60-135
	Neefe et al. (334)	1946	Icteric	Oral	10	–	–	–
	Neefe et al. (336)	1944	Incubation (-87 days)	Parenteral	2	2	–	–
	Paul et al. (357)	1945	Incubation (-60 days)	Parenteral	8	3	–	94-132
Nasopharyngeal wash	Findlay and Martin (124)	1943	Icteric	Intranasal	4	3	–	28-50
	Mac Cullum (281)	1945	Icteric	Intranasal	17	2	–	100
	Neefe at al. (334)	1946	Icteric	Intranasal and oral	4	–	–	–
Urine	Neefe et al. (334)	1946	Icteric	Oral	1	–	–	–

A growing tendency to see epidemiological studies as a hierarchy of methods, conferring greater scientific value to experimental randomized studies and less value to observational studies must also be subject to discussion.

Informing volunteers on possible hazards and damages to health as a result from experiments is a delicate task since there is always a margin of uncertainty for the researcher himself. To act ethically we must consider the principle of precaution for it is not always possible to evaluate risks as precisely as we would like to.

This principle in relation to prevention of hepatitis has been recently discussed by Harvey J. Alter[33], co-discoverer of the Australia antigen and receiver of the *Lasker Award* for the study that led to the discovery of HCV and the development of screening tests that reduced transfusion hepatitis to almost zero[34]. Koch and Evans postulates are insufficient for today's standards. The non-reproduction of hepatitis *in vitro* was overcome by electron microscopes and molecular biology that made possible the identification of HAV and HCV. The lack of application of the principle of precaution, or protection as referred by Schramm et al.[8], may be contributing to the transfusional transmission of hepatitis in scientific research and in biomedical procedures, due to the lack of substitution of old methods by newer

and safer technology, as determined by CNS Resolution 196/96[7]: "the principal investigator must stop the protocol immediately when any risk or damage to the health of the research subjects, not exposed in the informed consent and consequent to research procedures, is detected" and "as soon as the advantage of a procedure over another is detected, the protocol must be suspended and the best procedure must be offered to all research subjects".

Keeping pace with scientific changes the legislation on the ethics of research must be reviewed to consider the uncertainty implied on the information given to volunteers and the possibilities of hazard[30,35]. Moreover, it is not enough that the legislation be regularly reviewed, but the investigator must exercise his responsibility by being ahead of the legislation when the preservation of the health and well being of the research subjects may be at issue.

Resistance to reformulation of scientific concepts

The history of adverse effects of yellow fever vaccination of American soldiers in World War II offers a unique opportunity to discuss how the resistance to reconsider concepts and to change processes of production of pharmaceutical products may cause irreversible damage to health and retard the implementation of precautionary measures of control[36,1,33].

Since the 1930s, Findlay et al.[4] had shown evidence of association between yellow fever vaccination and hepatitis and proposed that the vaccine be produced without the use of human serum. But it was only during World War II - when there were 28,585 cases of jaundice in American and other troops, with 62 deaths; and the American government and the scientific community became the targets of a hot press debate – that changes in the process of vaccine production were introduced[36].

Other examples of this scientific resistance are the long intervals between the recognition of transfusional transmission of HBV and HCV and the implementation of preventive measures: 30 and 15 years respectively. According to Alter[33]: "This statement is being made not to cast retrospective blame, but to take a lesson from history and to illustrate the value of having a protective preemptive mechanism in place before the next agent strikes."

Conclusions

This brief historical view of the informed consent, focused on the case of hepatitis, points to its unequivocal role in the assurance of the autonomy of research subjects. But, it also leads us to ask if it is sufficient to preserve these subjects from hazards. The answer seems to be no.

We have shown factors that can interfere with free and informed consent of research volunteers. The complexity involved in the acceptance or refusal to be the subject of research must be considered by Ethics Committees and adequate means must be developed to further advance the protection of research subjects. An important component for the preservation of the social value of scientific research is strict adherence to the legislation that aims to protect society.

Informed consent aims to protect and preserve the health of the research subjects and cannot be reduced to an instrument for the preservation of the integrity of research protocols. The responsibility of the researcher and the institution cannot be restricted to these protocols, to preserve the credibility of both. The researcher also needs to be informed and to feel free to interrupt the research when he suspects that it may be causing harm to the subjects.

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