

SPECIAL ARTICLE

The Willowbrook Hepatitis Studies Revisited: Ethical Aspects

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Studies of the natural history and prevention of viral hepatitis were initiated at Willowbrook State School in 1955. During the subsequent two decades there was considerable controversy regarding the ethical aspects of these studies. The background of these studies is described in detail in historical context. This report should provide the reader with information needed to make an independent objective judgement of the ethics of the Willowbrook hepatitis studies.

During the first half of this century, outbreaks of various infectious diseases were prevalent in orphanages, military barracks, and institutions for mentally retarded children. These outbreaks involved highly susceptible populations living in conditions of overcrowding and poor hygiene. Certain infectious diseases, such as influenza and measles, occurred as epidemics at variable intervals. Other infections, such as shigellosis and hepatitis, were generally endemic in nature.

During the mid-1950s my colleague, Dr. Robert Ward, and I were invited to join the staff of Willowbrook State School as consultants in infectious diseases. This institution for mentally retarded children had been plagued by the occurrence of such epidemic and endemic diseases as measles and hepatitis. Our efforts during the next two decades were devoted to the control of these infectious diseases.

In 1960 an epidemic of measles swept through Willowbrook, leaving 60 children dead. The studies that we initiated with the live attenuated measles vaccine developed by Dr. John Enders and his colleagues culminated in the eradication of measles from the institution by the end of 1963.

Hepatitis, which affected virtually every child in Willowbrook as well as many employees, proved to be a more difficult problem. It was essential to acquire new knowledge about the natural history of this disease—knowledge that might lead to its ultimate control.

The studies during the subsequent two decades

were perceived by some critics to be unethical. As a matter of fact, in recent years the name “Willowbrook” has become synonymous with medical research gone astray. With time, facts have become distorted or forgotten, leaving only emotions.

Thirty years have elapsed since the Willowbrook hepatitis studies were initiated in the mid-1950s. I am as convinced today as I was at that time that our studies were ethical and justifiable. This judgement is based on knowledge of the extraordinary conditions that existed in the institution as well as on an assessment of the potential risks and benefits for the participants. The purpose of this article is to discuss the ethical aspects of our studies, within their appropriate historical context. It is hoped that this information will enable the reader to make an independent, objective judgement as to the ethics of the Willowbrook studies.

Establishment of the Willowbrook State School

In 1938 the New York state legislature perceived the need for an additional institution for the care of mentally retarded children. It allocated funds to purchase 375 acres of land located at Willowbrook on Staten Island and authorized the construction of facilities to care for 3,000 mentally retarded children from the greater-New York metropolitan area. The institution, completed in 1942 and designated Willowbrook State School, was taken over by the federal government to meet an urgent need for an army hospital to care for disabled military personnel from World War II. The U.S. Army Medical Corps renamed it the Halloran General Hospital in honor of the late Colonel Paul Stacey Halloran, a U.S. Army medical corpsman.

After the war ended in 1945, there was consider-

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able political pressure to retain Halloran General Hospital as a Veterans Administration hospital. The conflict between the needs of the Veterans Administration and the needs of the New York State Department of Mental Hygiene was described in the following letter sent by Governor Thomas Dewey to General Omar Bradley, who was director of the Veterans Administration at that time.

Every year in the State of New York, thousands of children come into this world who are mentally and physically defective and feeble minded, who never can become members of society. They require constant care, both medically and physically, and in many cases, for social, psychological and economic reasons, few parents can afford to place them in private institutions. Even if such institutions existed in sufficient quantity, the result is that the state must take responsibility for the care of these children and do so with a high degree of tenderness and attention.

At present, the State of New York operates two downstate institutions for the care of such infants and children. One is the Wassaic State School in Dutchess and the other is Letchworth Village in Rockland County. There are several other state schools for mental defectives but they are too overcrowded and none is or can be equipped for the additional care of infants.

Hundreds of infants and children unable to care for themselves are sleeping on mattresses on floors of these institutions. What is more serious is that there are eight to nine hundred infants on the waiting list for admission and the State Commission of Mental Hygiene daily must deal with distracted parents who seek to have their children placed in state institutions. The mail of the Commissioner of Mental Hygiene is filled with letters from such parents, many of whom are veterans.

It seems to me that we are now confronted with these two conflicting obligations at Willowbrook. The first is that of the Federal Government to provide hospital care for its veterans after they are discharged from service. The second is the obligation of the State of New York to provide care for permanently helpless infants. Obviously, Willowbrook cannot be used for both.

Finally, on October 24, 1947, after a delay of five years, 10 patients from Wassaic State School and 10 patients from Letchworth Village were transferred to Willowbrook State School. Initially, patients were both transferred from other institutions and admitted from the community. In retrospect, it is apparent that the infectious diseases endemic in Wassaic

State School and Letchworth Village were introduced into Willowbrook by patients who were transferred from these institutions.

Recognition of Hepatitis as an Endemic Disease

The occurrence of so-called infectious hepatitis was first observed in 1949. Later, in response to extraordinary pressure from many parents, the patient population increased rapidly in subsequent years; it exceeded 3,000 in 1953, 4,000 in 1955, and eventually it exceeded 6,000. In his report to a joint legislative committee on mental and physical handicap, the late Dr. Jack Hammond, director of Willowbrook State School stated:

The overcrowded conditions in the buildings make care, treatment, supervision and possible training of the patients difficult, if not impossible. When the patients are up and in the day rooms, they are crowded together, soiling, attacking each other, abusing themselves and destroying their clothing. At night in many of the dormitories the beds must be placed together in order to provide sufficient space for all patients. Therefore, except for one narrow aisle, it is virtually necessary to climb over beds in order to reach the children.

The residents of Willowbrook State School were the most severely retarded, the most handicapped, and the most helpless of those being cared for in the New York state system. The population of about 6,000 included 77% who were severely or profoundly retarded, 60% who were not toilet trained, 39% who were not ambulatory, 30% who had convulsive seizures, and 64% who were incapable of feeding themselves. Thus, the conditions were optimal for the transmission of hepatitis, shigellosis, respiratory infections, and parasitic infections.

By the early 1950s the director of Willowbrook and his staff were convinced that serious overcrowding and an inadequate staff were in great part responsible for the increasing hepatitis problem. Their statistics indicated that the annual attack rate of hepatitis with jaundice was 25 per 1,000 among the children and 40 per 1,000 among the adults. Efforts to correct this intolerable situation were unsuccessful. Society had created a problem, but it provided no solution. It was during that period that my colleague, the late Dr. Robert Ward, and I were asked to join the staff of Willowbrook as consultants in infectious diseases. We were not qualified to deal with the so-

cietal problems, but we believed that we could help control the existing medical problem of hepatitis.

Identification of the Hepatitis Problem in Willowbrook

Our first objective in 1955 was to carry out an extensive epidemiologic survey. We were fortunate because new tests to detect hepatic dysfunction were described that year, namely, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). These sensitive assays enabled us to detect the presence of hepatitis without jaundice (anicteric hepatitis). Today, SGOT is called alanine aspartate transaminase (AST), and SGPT is called alanine aminotransferase (ALT).

Our colleague, the late Dr. Joan P. Giles, joined us during this period. During the course of our epidemiologic surveys and the performance of routine physical examinations, she collected many thousands of serum specimens. Instead of discarding them—the usual practice in most laboratories—we stored them in an increasing number of deep freezers. The scientific dividends of this serum bank proved to be incalculable in later years.

After the results of the SGOT and SGPT assays were reviewed, it was obvious that the detected cases of icteric hepatitis represented the tip of a hepatitis iceberg. The results of these highly sensitive tests of liver dysfunction convinced us that most newly admitted children were destined to contract hepatitis infection under the conditions that existed in the institution. The occurrence of hepatitis among Willowbrook children was as predictable and inevitable as the occurrence of respiratory infections among children in day care centers.

During the course of our epidemiologic survey in 1955, all of the evidence indicated that the endemic disease was so-called infectious or type A hepatitis, an infection that spread via the fecal-oral route. The disease was mild and there were no deaths. Although the same disease was more severe and more debilitating in the adult employees, they, too, recovered completely. Previous experience of various investigators had revealed that hepatitis A was much milder in children than in adults. Efforts to reduce the overcrowded conditions at Willowbrook continued to be unsuccessful. In a desperate attempt the director mailed letters to about 5,000 parents, requesting that they return a questionnaire that contained the statement, “I wish to discuss the possibility and advis-

ability of removing my child from Willowbrook State School so that he/she can live at home.” A total of 24 parents responded, and only two children were taken home at that time!

The Willowbrook Hepatitis Studies

After one year of careful observation and study in 1955, we concluded that the control of hepatitis in Willowbrook could be achieved if it were possible to devise and conduct well-designed studies to shed new light on the natural history and prevention of the disease—new knowledge that could conceivably lead to the development of a vaccine. Thus, our decision to propose the exposure of a small number of newly admitted children to the endemic Willowbrook strain of hepatitis virus was reached after serious consideration of the following factors and assumptions:

(1) As indicated previously, under the conditions existing in the institution, most newly admitted children would contract hepatitis. This empiric impression was confirmed in the 1970s when newly developed serologic tests revealed that >90% of the residents of the institution had hepatitis A and B markers of past infection.

(2) Hepatitis was known to be especially mild in the three- to 10-year age group that would participate in the studies. Our extensive survey confirmed that most infections were inapparent or benign and there were no deaths.

(3) The artificially induced infection would induce immunity to the endemic strain of hepatitis virus and, we hoped, to other strains that might be introduced by new admissions or transfers to Willowbrook. Studies in the 1940s had revealed that hepatitis A infection was followed by homologous immunity. Therefore, the artificially induced infection would be prophylactic.

(4) The children would be admitted to a specially equipped, specially staffed unit where they would be isolated from exposure to other endemic infectious diseases occurring in the institution—namely, shigellosis, respiratory infections, and parasitic infections.

(5) Only children whose parents gave consent would be included. Our method of obtaining informed consent changed progressively during the course of the studies. In 1956 the information was conveyed to individual parents by letter or personal interview. Later, we adopted a group technique of

obtaining consent. First, a psychiatric social worker discussed the project with parents during a preliminary interview. Those who were interested were invited to attend a group session at the institution to discuss the project in greater detail. These sessions were conducted by our staff responsible for the program, including Dr. Giles, the supervising nurse, staff attendants, and psychiatric social workers. Meetings were often attended by outside physicians who had expressed interest. Parents, in groups of six to eight, were given a tour of the facilities. The purposes, potential benefits, and potential hazards of the program were discussed with them, and they were encouraged to ask questions. Thus, all parents could hear the response to questions posed by the more articulate members of the group. After leaving this briefing session, parents had an opportunity to talk with their private physicians, who could call Dr. Giles for more information. Approximately two weeks after the visit, the psychiatric social worker contacted the parents for their decision. If the decision was in the affirmative, the consent was signed, but parents were informed that consent could be withdrawn at any time. It was clear that the group method enabled us to obtain a more thorough informed consent. Children who were wards of the state or children without parents were never included in our studies.

From 1956 the protocols were reviewed and sanctioned by various local, state, and federal agencies. These studies were reviewed and approved by the New York University and Willowbrook State School committees on human experimentation after their formation in February 1967. Prior to this date, the functions of the present Institutional Review Board were performed by the Executive Faculty of the School of Medicine for studies of this type. The initial proposal in 1956 was reviewed and approved by the following groups: Executive Faculty, New York University School of Medicine; New York State Department of Mental Hygiene; New York State Department of Health; and Armed Forces Epidemiological Board. It is of interest that the guidelines that were adopted for the hepatitis studies at their inception in 1956 conformed to the World Medical Association's draft Code of Ethics on Human Experimentation, which was presented to its general assembly in September 1961, five years later. It is also of interest that our established policy of informed consent was instituted at least 10 years before it was mandated by most research institutes and medical centers in the United States.

During the period 1956–1967, we believed that we were dealing with endemicity of hepatitis A, an infection that should be followed by lasting immunity. However, by 1967 it was obvious that many children had had two attacks of hepatitis. Our studies of this phenomenon revealed that one attack was caused by the so-called MS-1 strain of hepatitis virus and the second attack, by the MS-2 strain. Thus, it became apparent that two types of hepatitis were endemic in Willowbrook—MS-1, resembling hepatitis A, and MS-2, resembling hepatitis B. By 1969, after Blumberg discovered the Australia antigen, the new technology enabled us to confirm that Willowbrook MS-2 serum contained hepatitis B antigen.

Our serum bank contained specimens obtained from most patients who contracted naturally acquired hepatitis during the period 1956–1969. When we tested these serum specimens in the 1970s, using the newly developed serologic assays, it was obvious that both hepatitis A (MS-1) and hepatitis B (MS-2) had been endemic in the institution since 1956. It was also apparent that hepatitis B, like hepatitis A, was generally a mild or inapparent infection in Willowbrook children. A retrospective diagnosis was made by testing the sera for the presence of hepatitis B antigen and abnormal serum transaminase values. During the course of this new survey, we found that most children had markers of present or past hepatitis B infection. Thus, it was likely that newly admitted children would be intensely exposed to both types of hepatitis. When this new information was presented to the members of the Commission on Viral Infections of the Armed Forces Epidemiological Board in 1969, they agreed that the studies should be continued.

It should be emphasized that the studies were conducted in Willowbrook State School because hepatitis was a severe problem in this institution and not, as some charged, because we were looking for a facile "guinea pig" population. The fact that the children were mentally retarded was relevant only to the extent that society placed them in an institution where hepatitis was prevalent. The primary objective of our studies was to protect the children and employees while acquiring new knowledge in the process.

Summary of Contributions of Willowbrook Hepatitis Studies

The accomplishments of the Willowbrook studies

are well documented in the medical literature (see Bibliography, below). They include:

(1) *Identification of two distinctive clinical, epidemiologic, and immunologic types of hepatitis, MS-1 (type A) and MS-2 (type B).* The serum specimens collected from patients with MS-1 and MS-2 infection provided many investigators with “pedigreed” sera known to be specific for hepatitis A or B. After the discovery of Australia antigen by Blumberg and colleagues, the use of these clinical samples by various investigators established the association between Australia antigen and hepatitis B virus.

(2) *Demonstration that hepatitis B infection is transmitted by intimate contact and oral as well as parenteral exposure.* Previously, it was believed that percutaneous inoculation with contaminated needles, blood, or blood products was essential for the transmission of hepatitis B. It is well recognized today that hepatitis B is a sexually transmitted infection and it is spread by intimate physical contact and transfer of body fluids.

(3) *Demonstration that hepatitis B immune globulin is effective for the prevention of type B hepatitis.* The results of this study led to the initiation of several large multicenter trials to determine the efficacy of HBIG in preventing hepatitis B among such high-risk individuals as hemodialysis staff and patients, newborns of HBsAg-positive mothers, sexual contacts of patients with acute hepatitis B, and persons accidentally inoculated with HBsAg-positive blood by needle-stick exposures.

(4) *Development of the first prototype inactivated hepatitis B vaccine.* It was demonstrated that a boiled 1:10 dilution of MS-2 serum in distilled water was not infectious, but it was immunogenic and protective. These studies, published in 1970, clearly demonstrated the feasibility of developing a hepatitis B vaccine and stimulated various investigators to prepare inactivated vaccines from the plasma of chronic hepatitis B carriers.

Conclusion

While I agree with the critics of medical research who state that the ends (successful accomplishments) do not justify the means, I believe that this generalization does not apply to our Willowbrook studies. Under the conditions that existed in the institution, all children were constantly exposed to the naturally acquired hepatitis viruses. Moreover, the overall risk

for children in our special isolation unit was less than the risk for other children who were admitted to buildings in the institution where shigellosis and respiratory infections, as well as hepatitis, were endemic.

A century ago Claude Bernard defined the limits of human experimentation. He stated that

it is our duty and our right to perform an experiment on man whenever it can save life, cure him, or gain some potential benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result may be highly advantageous to science or to the health of others. But performing experiments and operations exclusively from the point of view of the patient's own advantage does not prevent their turning out profitably to science.

My colleague, the late Dr. Joan P. Giles, expressed it beautifully and succinctly in her letter to the *Lancet*, published May 29, 1971, in which she said, “A farmer may pull up corn seedlings to destroy them or he may pull them up to set them in better hills for better growing. How then does one judge the deed without the motive?” This describes the motivation for our studies at Willowbrook State School.

I am greatly indebted to many collaborators, colleagues, and organizations for support and encouragement during the course of our Willowbrook hepatitis studies:

To the late Dr. Robert Ward, who was the principal investigator of our studies from 1956 to 1958. He was an outstanding investigator and a colleague who had exceptional human qualities.

To the late Dr. Joan P. Giles, who died of cancer in 1973 after devoting 17 years of her life to the care of the children in our hepatitis unit. She was a highly ethical physician and a person of great humanity and integrity.

To Harriet Friedman and Cass Lattimer, research associates, for more than 25 years of competent and meticulous work in our laboratory.

To the late Dr. Jack Hammond, director of Willowbrook State School. He and his dedicated staff labored under the most difficult circumstances. They were subjected to incredible abuse by certain representatives of the news media and by publicity-seeking legislators who criticized them for the horrible conditions in the institution. Their morale was devastated because they knew that the pressures of society (distraught parents and their legislators) were

responsible for increasing the census to more than 6,000 in a 3,000-bed institution. It was "society" that was responsible for the overcrowded, unhygienic conditions in Willowbrook, not the dedicated people who worked there under stressful conditions.

To the late Dr. John R. Paul and Dr. Robert McCollum of Yale University for their encouragement and wise counsel during the 1950s and 1960s.

To the Armed Forces Epidemiological Board and the U.S. Army Medical Research and Development Command for 25 consecutive years of financial support.

And, finally, to many loyal and devoted colleagues and friends whose support helped ease the pain inflicted by many vicious attacks during the late 1960s and early 1970s. We were especially grateful to the parents of the Willowbrook chapter of the Benevolent Society of Retarded Children for the plaque that they presented to us at their 1967 annual meeting. The inscription on the plaque stated, "In recognition of distinguished, pioneering, humanitarian research in the prevention of infectious diseases and their resultant complication in children, born and unborn."

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