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Exclusive: The Willowbrook Hepatitis Project

Studies With Children Backed On Medical, Ethical Grounds

Medical Tribune Staff Report

NEW YORK—In the current headline-making rounds of accusations and rebuttals about patients in public hospitals here being used as "guinea pigs" for medical research, no one has had a harder time explaining their position than the investigators at Willowbrook State School.

The accusation they face, made by a legislator in a speech on the floor of the State Senate, is that 500 or more men-

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tally retarded children at Willowbrook were injected with live hepatitis virus in a research program.

The only part of the accusation they can refute outright is the number of children in the study—"it's a little more than 250, not 500," one of the investigators said.

Otherwise the legislator's original charge is essentially correct—as far as it goes. A principal spokesman for the Willowbrook investigations told MEDICAL TRIBUNE, "It's hard to defend yourself against a half-truth. You can tell the other half of the truth but that doesn't do it."

In his initial speech on the subject, State Sen. Seymour R. Thaler, Democrat from the Queens section of New York City, said nothing about whether consent had been obtained from parents of children in the Willowbrook study.

When the Willowbrook investigators avowed that parental consent had been obtained, Senator Thaler replied that parents had no right to sign their children into a medical research project. In addition, he said, physicians have no right to give a disease to a child in order to study the disease.

Putting his views into legal form, Senator Thaler a few days later introduced a

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bill that would preclude the use of children in medical research except in an unspecified emergency situation. The measure also would demand "informed consent" in writing from any adult entering a research program.

With the Willowbrook project brought into public controversy as an example of a medical investigation whose mere description sounds damning, MEDICAL TRIBUNE essayed to find out more precisely what the program is doing and where it might stand in regard to the ethical tenets of human experimentation.

The Willowbrook study has been going on for 11 years. For two years before that, a survey was conducted at Willowbrook to establish definitely what had become a distinct clinical impression to some of the institution's medical staff — that infectious hepatitis was endemic there.

The director of the hepatitis project since its inception has been Dr. Saul Krugman, Professor of Pediatrics and department chairman at New York University School of Medicine. He describes Willowbrook, a sprawling facility at the edge of a woodland belt on Staten Island, as "probably unique" for an investigation of this kind.

"Willowbrook was not chosen because its population was mentally retarded," Dr. Krugman said, "but because it had endemic infectious hepatitis and a sufficiently open population so that the disease could never be quieted by exhausting the supply of susceptibles." The patient population is nearly 5,500, a total that Dr. Krugman believes is the biggest in any one facility for the mentally retarded in the U.S.

Most Patients Are Children

In addition, he said, Willowbrook's patients are predominantly children; a few years ago the median age was 12, today it is slightly lower because the only general admissions have been to the infant facilities—the only buildings not overcrowded.

"It was well recognized," Dr. Krugman said, "that infectious hepatitis was a mild and relatively benign disease in children as compared with adults. Experience at Willowbrook indicated that the disease observed there was especially mild. Consequently only the Willowbrook strains of infectious hepatitis would be used for the study."

With the preliminary survey pointing to Willowbrook as a feasible place to investigate hepatitis immunity, Dr. Krugman organized his study plans and presented them to the N.Y.U. Committee on Human Experimentation, to the state Department of Mental Hygiene (which operates Willowbrook), and to the Armed Forces Epidemiological Board (whose sanction was needed if the project was to get supporting funds from the military).

DR. KRUGMAN

All three bodies approved the study, and financial support came in what would be the first of a series of contracts from the Army's Research and Development Command.

According to plan, a 16-bed isolation unit was set up at Willowbrook, complete with its own kitchen and ward attendants. The idea was to protect the study subjects from Willowbrook's other endemic diseases—such as shigellosis, measles, rubella, and respiratory and parasitic infections—while exposing them to hepatitis.

Aside from the obvious emotionally inflammatory aspects of the study, the principal ones being that the subjects are children and mentally retarded, the factor in the Willowbrook investigation that has drawn the most fire for a number of years

is that subjects are deliberately induced to acquire a disease.

"That sounds bad when you say it that way," Dr. Krugman acknowledged. "But it's just as important to mention that at Willowbrook it has been inevitable that most newly admitted children will become infected [with hepatitis] in the first six to 12 months after entering the institution."

This intense exposure of Willowbrook patients to infectious hepatitis meant that study subjects had to be drawn from outside the institution's population to provide a reasonable chance they would be susceptible to the disease.

The investigators took the obvious course: they proposed the study to parents of retarded children who had been accepted but not yet admitted to the school. The first contact was made by a psychiatric social worker in the course of processing applicants. "If the parents were interested, then they talked to a member of the investigation's medical staff," Dr. Krugman said.

What Are Parents Told?

This usually was Dr. Joan Giles, Research Associate Professor of Pediatrics at N.Y.U., who has been on duty full-time at Willowbrook since the hepatitis study began. What does Dr. Giles tell parents?

"I give as full an explanation as I can," she said. "And there are a lot more positive things to tell them now than there were 11 years ago. I explain that there is no vaccine against infectious hepatitis, that the disease is always present here, and that their child is quite likely to come in contact with it by the intestinal-oral route common to a close-quartered group of this type.

"I also tell them that we can modify the disease with gamma globulin but we can't provide lasting immunity without letting them get the disease. I explain that we use blood serum taken from Willowbrook patients who had hepatitis and that experience has shown a minimum dosage that can induce the disease in a form even less severe than occurs naturally in patients outside the hepatitis unit."

Concerning the risks, Dr. Giles said she explains what hepatitis can do when it progresses to a severe stage. And she may also explain what jaundice is. But, in addition, she mentions that there is no evidence that the artificially induced disease has ever caused permanent damage to any of the study subjects, that the incidence of jaundice has been well controlled with gamma globulin, and that most of the hepatitis cases in the unit "are hard to tell from the sniffles unless you know what you're looking for."

At the end of her briefing and after any questions have been answered, Dr. Giles said she advises the parents to ask their family physician for his opinion on the program. "Some doctors have called me with a few more questions," she said, "but usually the parents are willing to sign the consent form after they talk with me."

With few exceptions, according to Dr. Krugman, this has been the procedure for obtaining parental consent in the hepatitis program since it began. Written permission has been secured for every child enrolled in the study. On the average, a new study group is begun every three months. The number of children in each group ranges from six to 14; their ages have run between three and 10 years.

Serum Taken From Patients

All serum used in the study has been taken from Willowbrook patients early in their hepatitis episode. It is inoculated into suckling mice and four different tissue cultures to rule out the possibility of other viral or mycotic agents, Dr. Krugman said. Then it is injected as straight serum, not concentrated, into the study subjects. Dosage volumes have ranged from 0.25 ml. down to 0.025 ml. The result of the injection is that the susceptible children get infectious hepatitis. In most of them, said Dr. Giles, the only way to be certain they have it is to run serum transaminase tests. Jaundice occurs in about 8 per cent of the subjects. Dr. Krugman said the jaundice was "very transitory . . . very slight, and frequently only Dr. Giles can recognize that the child is jaundiced." In the general patient population at Willowbrook, the incidence of jaundice with hepatitis is 15 per cent.

Children remain in the isolated hepatitis unit for about two months, which more than covers the incubation period for the common type A strain (30-40 days). When all liver chemistry tests have returned to normal, the subjects are moved to an observation ward for another month or so, partly to guard against the possibility that they might be harboring an infrequent type B strain whose incubation period ranges as high as 80 days or more.

What has the Willowbrook study provided in the way of research benefits?

According to Drs. Krugman and Giles, there has been much time spent on evaluating dosages—both of the minimal amount of virus-containing serum needed to cause a mild form of the disease and of the optimum amount of gamma globulin that would allow the development of a passive-active immunity.

As a result, the investigators felt they knew enough about it to begin—last September—a routine program of GG administration to every new patient at Willowbrook. One injection is given on admission, and a second four months later. The best dosage range appears to be 0.01 or 0.02 ml. per pound. The program has cut the incidence of icteric hepatitis among patients by 80-85 per cent, according to Dr. Krugman. A similar reduction in the icteric form of the disease has been accomplished among the employees, who began getting routine GG earlier in the study.

The Willowbrook results also have paid off for the armed forces, Dr. Krugman said. Troops going to areas of endemic hepatitis, such as Vietnam, now routinely get 0.05-ml./pound of GG on much the same schedule as used at Willowbrook. The same regimen also has been applied to Peace Corpsmen.

There still is no vaccine against hepatitis, Dr. Krugman said, but the Willowbrook experiments are aiding in many attempts to isolate the hepatitis virus. "One cc. of serum taken from our subjects early in the disease is enough for a year's isolation work in most laboratories," he said. At least four other laboratories in the country, in addition to his own, are trying to isolate the Willowbrook hepatitis virus. "Since it seems to be naturally attenuated," said Dr. Krugman, "it would appear to be the best starting material toward a vaccine."

Study Criticized in 1965

The Willowbrook hepatitis study was a target for criticism long before Senator Thaler precipitated the current excitement about it. In the spring of 1965, Dr. Henry K. Beecher of Harvard used it as one of many examples of "questionable ethical studies"—the question lying largely in the matter of "experimentation on a patient not for his benefit but for that, at least in theory, of patients in general."

Again last summer, Dr. Beecher, who is a Professor of Research in Anesthesia, cited the Willowbrook study among 22 examples in an article in the *New England Journal of Medicine*. Of the study he wrote, "There is no right to risk an injury to one person for the benefit of others."

By way of reply, Dr. Krugman said that he was "certain from the outset" that there would be criticism of the program. "We set it up very carefully . . . and in accordance with the World Medical Association's Draft Code of Ethics on Human Experimentation." That code, more commonly known as the Declaration of Helsinki, has been endorsed by a large number of national medical organizations, including the American Medical Association and seven other medical groups in the U.S.

On the matter of informed consent, Dr. Krugman said he believes the investigation has "been more than cautious" in obtaining written parental consent only after they understood the program to their apparent satisfaction. For instance, he said, "we decided at the start to use no wards of the state, although by law the administrator of Willowbrook could have signed consent for them."

Still, the obtaining of consent at Willowbrook has not been without controversy. Dr. Jack Hammond, administrator of the institution, said the "biggest fuss" arose more than a year ago over a "complete misinterpretation . . . of an unfortunate coincidence."

The circumstances were set up by the closing of Willowbrook in late 1964 to all new admissions because of overcrowding. Parents who applied for their children to get in were sent a form letter over Dr. Hammond's signature saying that there was no space for new admissions and that their name was being put on a waiting list.

New Patients Were Admitted

But the hepatitis program, occupying its own space in the institution, continued to admit new patients as each new study group began. "Where do you find new admissions except by canvassing the people who have applied for admission?" Dr. Hammond asked.

So a new batch of form letters went out, saying that there were a few vacancies in the hepatitis research unit if the parents cared to consider volunteering their child for that.

In some instances the second form letter apparently was received as closely as a week after the first letter arrived. "All of a sudden," Dr. Hammond recalled, "we had parents' meetings, calls from local politicians, calls from family physicians . . . all sorts of kicks."

Canvassing the parents by letter "obviously was open to misinterpretation, so we stopped it more than a year ago," Dr. Hammond said.

But the repercussions have not stopped. Most recently an educator who works in rehabilitation programs for the mentally retarded, Jack M. Gootzeit, Ed.D., appeared on a New York City television news program to charge that the form letters constituted a "high-pressure method" of obtaining consent from parents "desperate to institutionalize their child."

In the midst of the current ruckus, Dr. Hammond happily recalls one instance in which an incipient investigation of the Willowbrook hepatitis project reached what he called a "logical conclusion."

"Senator [Robert F.] Kennedy sent a man around to check on the program," the administrator said. "I sent him to Dr. Krugman for a full explanation, and he went away satisfied that everything was what we said it is."