

Immunization Is Reported In Serum Hepatitis Tests

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By LAWRENCE K. ALTMAN

Researchers at New York University Medical Center reported yesterday that they had apparently succeeded in immunizing a small group of children against serum hepatitis in a series of continuing experiments.

Serum hepatitis, one of the two basic forms of the liver-damaging disease generally known as hepatitis, can be spread by blood transfusion.

The serum type is said to affect more than 150,000 Americans each year and to kill about 3,000, often those weakened by other diseases.

The report was made by Dr. Saul Krugman, head of the research team, to an excited audience of hepatitis experts, physicians and medical students who packed the center's auditorium at 550 First Avenue.

It was an emotion-charged atmosphere in which many felt that an important basic step had been taken in combating a ravaging disease.

But the researchers emphasized that their results were preliminary, that they had injected just a few children for investigational purposes only,

and that more time was needed to evaluate the duration of the protection provided.

They expressed the hope, however, that their immunizations would ultimately lead the way to a vaccine for prevention of serum hepatitis.

Like vaccines against other infectious diseases, the researchers said, extensive testing of the hepatitis immunizations is required before such agents can qualify for approval by the Division of Biologics Standards at Bethesda, Md., the Federal agency responsible for such licenses.

When available, immunization would be used only for prevention of hepatitis, the doctors said, since it would not benefit a patient after the disease had made him lose his appetite, damaged his liver cells and turned his eyes and skin yellow.



The New York Times
Dr. Saul Krugman at the
N.Y.U. Medical Center.

The results of the researchers' studies, which had been presented to a closed scientific meeting in Washington earlier this month, amplified reports that they had published recently in the Journal of Infectious Disease and the Journal of the American Medical Association.

Dr. Krugman said that he was worried about declining Federal support for all medical research and that this had led him to take the unusual step of publicly announcing his group's findings before further publication in medical journals.

Team of Researchers

Dr. Krugman is professor and chairman of the department of pediatrics at the medical center. His co-workers were Dr. Joan Giles, a research pediatrician, and Dr. Jack Hammond, who directs the Willowbrook State School, an institution for mentally retarded people, on Staten Island.

Federal research cutbacks on the National Institutes of Health, Dr. Krugman said, threaten the solution of the riddle of serum hepatitis and other diseases.

Serum hepatitis has been a major public health problem throughout the world at least since 1883, when Dr. A. Lurman was credited with first describing a group of such cases in Germany.

A variety of viruses and chemicals such as drugs and alcohol can cause hepatitis, which means inflammation of the liver. When people speak of hepatitis, generally they mean the illness caused by one of at least two viruses.

Doctors recognize two types of viral hepatitis — infectious and serum—that they can distinguish only by the length of their incubation periods.

Infectious hepatitis — which affects tens of thousands of Americans, with some fatalities — usually takes weeks to make a person ill, whereas serum hepatitis generally takes months to produce its damage to the its critical role in regulating liver. Man needs this organ for many of the body's chemical and energy reactions.

Much of the understanding of the distinction between how the types make Americans sick has resulted from studies done by Dr. Krugman's group at New York University and at Willowbrook during the last 15 years.

Willowbrook, like other institutions caring for mentally retarded people, has had a chronic epidemic of hepatitis since 1949. A total of 5,500 adults and children live in close contact at Willowbrook, which Dr. Krugman said was the largest such institution in this country.

Crowded living conditions contribute to the high rates of hepatitis and dysentery that exist at institutions such as Willowbrook. Hepatitis can be spread from person-to-person through improper sanitary methods. Also, it can spread through contaminated water and food.

Dr. Krugman stressed that hepatitis tends to be a much milder disease in children than in adults. Yet hepatitis in children is a serious public health problem because youngsters can become long-term carriers of the disease and spread it to adults. It is a serious problem among military troops.

The ethics of the studies that Dr. Krugman has done at Willowbrook have been criticized in the past by legislators like Senator Seymour R. Thaler, Democrat-Liberal from Queens, and by some physicians such as Dr. Henry K. Beecher, of Boston.

When reached in Albany yesterday Senator Thaler hailed the research and said he was now persuaded that the work was being properly conducted.

Dr. Krugman emphasized yesterday that his team had obtained written informed consent for the experiments from the parents of each of the children at Willowbrook. Also, he said, the studies always had been reviewed beforehand with Government officials in New York and Washington, D. C.

Consent From Parents

"Our method of obtaining informed consent has changed progressively since 1956," Dr. Krugman said.

Now, he said, the parents of the children accepted for admission to Willowbrook are invited to discuss in a group session the studies that the doctors do in a special area of the school.

Another scientist at the lecture, Dr. Alfred M. Prince of the New York Blood Center, paid tribute to Dr. Krugman's "courage and imagination" in doing the research and said that the N.Y.U. pediatrician had been "unjustly criticized."

Such hepatitis studies at Willowbrook and at other institutions need to be enlarged, Dr. Prince said.

Dr. Krugman said that the "crucial" factor involved in his group's studies was a protein called Australia antigen.

Dr. Baruch Blumberg and his associates at the Institute for Cancer Research in Philadelphia, discovered the protein in 1963 in an aborigine as part of genetic studies that they conducted in Australia.

Hence, Dr. Blumberg named the protein the Australia antigen. Subsequently, Dr. Blumberg's group linked the Australia antigen with hepatitis.

That discovery, a committee of the World Health Organization said recently, "has been the most spectacular advance in the seemingly insoluble problem of human hepatitis."

'Explosion of Knowledge'

About the same time, Dr. Prince detected at the blood center what he called serum hepatitis antigen in the blood of patients with the disease. Further testing showed that Dr. Prince's serum hepatitis and Dr. Blumberg's Australian antigens were identical.

"An explosion of knowledge" about hepatitis then resulted, Dr. Krugman said.

"The studies that the research reported yesterday were done on a total of 68 children, 3 to 10 years old. The children were admitted to Willowbrook in eight groups during the five-year period from 1965 to 1970.

Dr. Krugman said his group had tested two types of immunizations, both involving the Australia antigen, on these children.

One type was active immunization. By exposing the children to a heat-treated serum called MS-2, the doctors purposefully stimulated the youngsters' bodies to produce over a several-week period immunologic defense substances called antibodies.

The principle is the same as when doctors inject a killed virus vaccine against diseases such as influenza.

The other type was passive immunization, which protects through transfer of preformed antibodies such as those derived from a person who has recovered naturally from the disease.

This is the principle involved when doctors inject gamma globulin to protect individuals exposed to infectious hepatitis.

Supplies of gamma globulin are derived from blood donated by large numbers of individuals. The antibodies that people form after an attack of infectious hepatitis thus is pooled, or mixed, and used to modify the illness in persons exposed to the disease.

Gamma globulin generally has not proved effective in preventing serum hepatitis.

In the active immunization studies, Dr. Krugman used a boiled preparation of serum containing Australia antigen. After adding a small amount of water to prevent heated serum

from clotting, members of his team boiled the mixture for one minute.

This was just long enough to destroy its ability to cause disease. Yet this technique preserved the serum's ability to stimulate production of antibodies against Australia antigen in some children.

"Two inoculations were more effective than one," Dr. Krugman told the doctors, and "one inoculation gave enough protection to prevent some cases and to modify others."

Further, he said, "the individuals who received two injections of the boiled serum were not only protected against hepatitis but they also developed antibodies against the disease."

Serum Administered

The doctors said that they had given the boiled serum to 14 children at Willowbrook. Of the 10 children who received just one injection, four

were protected against serum hepatitis, Dr. Krugman said, whereas it modified "the hepatitis infection of the [other] six children."

"All four children" who received two injections of the boiled serum of four-month intervals, he said, "had significant protection against hepatitis during the 70-day period of observation."

Three children had no evidence of hepatitis. The doctors said they found laboratory evidence of hepatitis in the fourth child "on only one day."

The passive immunization studies, Dr. Krugman said, could not have occurred without the cooperation of Dr. Prince of the blood center at 310 E. 67th Street here. Researchers at that center, Dr. Prince said, are also conducting similar studies.

The World Health Organization noted that serum containing antibody to Australia antigen "has been extremely scarce." When it has been detected, the patient usually has been a hemophiliac, suffering from the genetic disease that prevents his blood from clotting normally after a cut or bruise.

Doctors suspect that hemophiliacs develop the antibodies from repeated exposures to the hepatitis virus from the hundreds of transfusions they have received to stay alive. Persons receiving scores of transfusions for other medical reasons could also develop such antibodies.

Hemophiliac Donor

From one hemophiliac who had an extraordinary high level of antibody to Australia antigen and who voluntarily donated the plasma portion of his blood during the last three years, Dr. Prince said he had prepared a small quantity of gamma globulin. The special gamma globulin has about 100,000 times the antibody found in the commercial supply of gamma globulin.

What the group did was to expose 15 children to serum containing Australia antigen, which from past experience they knew would have caused infection in almost every susceptible child.

The serum that the doctors used had been obtained from a child who got the identical type of hepatitis at Willowbrook.

But four hours after such exposure, the doctors gave the regular commercial gamma globulin to five children and the

hemophiliac's gamma globulin to the 10 others.

Dr. Krugman's team said that the hemophiliac's gamma globulin had proved "extraordinarily effective in preventing serum hepatitis" in the Willowbrook children.

"All 10 who received the special" globulin prepared from the hemophiliac were protected against hepatitis, Dr. Krugman said, but "the standard gamma globulin did not protect three of the five children who received it."

Dr. Prince cautioned his colleagues about the scarcity of the serum-hepatitis-antibody-rich gamma globulin. The entire supply has been allocated for the necessary research studies, he said, and "none is available for clinical use."

If the immunizations are licensed in the future on the basis of further evaluation, Dr. Krugman said they could be used to protect persons with a high risk of getting hepatitis.

Among such people would be patients knowing weeks in advance that they needed surgery and blood transfusions, such as for open heart operations.