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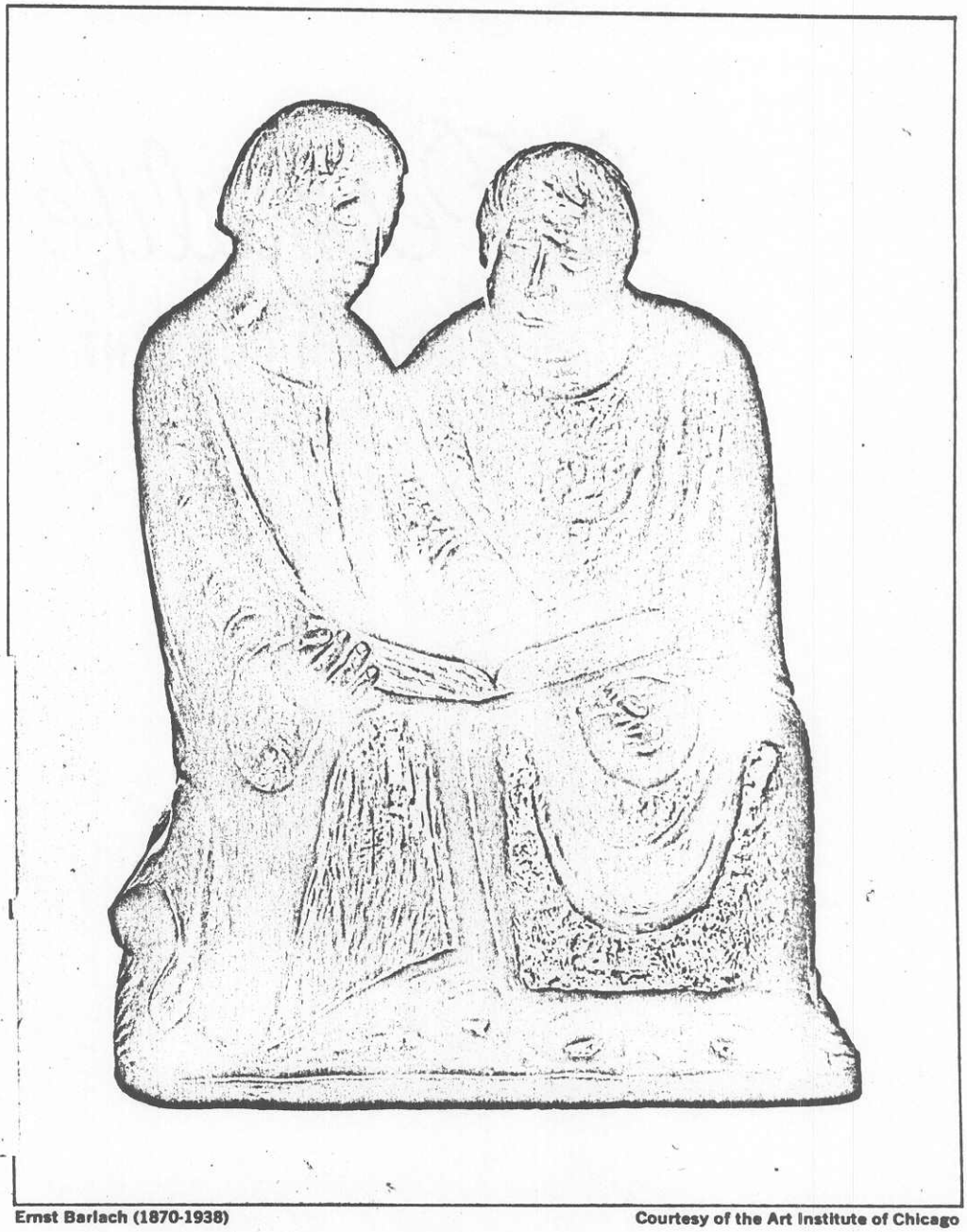

Ernst Barlach (1870-1938) Courtesy of the Art Institute of Chicago

Monks Reading

An advance is reported in quest for serum hepatitis vaccine

Active immunization against serum hepatitis has been achieved by a group headed by Saul Krugman, MD, professor and chairman of the Department of Pediatrics at New York University Medical Center.

In addition, the investigators have developed a procedure to confer passive immunity from accidental serum hepatitis infection, using a new, high-titer gamma globulin developed by Alfred Prince, MD, and his associates at the New York Blood Center.

The studies are preliminary, but are considered a significant step toward developing a vaccine for control of type B viral hepatitis, or serum hepatitis.

Other members of the group include Joan P. Giles, MD, research associate professor of pediatrics at New York University, and Jack Hammond, MD, director of the Willowbrook State School on Staten Island, NY. The group has been studying hepatitis since 1956.

Earlier, the investigators had observed that boiling for one minute serum made from the MS-2 (serum hepatitis) strain of virus destroyed the infective qualities of the substance without affecting its properties as an antigen. Dr. Krugman used a recent Honors Program lecture at the NYU Medical Center to describe the results of the new studies that suggest serum hepatitis can be prevented by active and passive immunization.

In ten children who received one inoculation of the inactivated MS-2 serum (0.2 ml of a 1:10 dilution), six developed hepatitis-associated antigen (HAA) and five had elevated SGOT levels approximately four months later when they were given untreated MS-2 serum.

"But the interesting observation is that five children developed detectable antibody," said Dr. Krugman. In five of the six children, the antigen appeared on the 42nd day after the second injection; no antibody was found in the sixth child until the 56th day.

A second group of four children had even more encouraging responses, Dr. Krugman said. These four received a second dose of inactivated MS-2 serum approximately 4½ months after the first, then were challenged four months later with the regular serum.

"All four developed antibody, three of the four

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Active immunization against hepatitis?

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had no antigen, and three had no elevated SGOT levels. One of the four had antigen present on only one day (the average duration may be many months), and one of the four had transaminase elevation on only one day," the investigator said.

"Under the conditions of this trial, at least, two inoculations (of the inactivated serum) seem to be immunogenic."

The children were residents of Willowbrook, a school for retarded children. Studies by the NYU group, confirmed by Dr. Prince's associates, indicate that children almost invariably are infected with both type A (infectious) and type B (serum) hepatitis within 6 to 12 months after entering such a school. (Hepatitis in children is a very mild disease, compared to the adult version.) Dr. Krugman stressed that the Willowbrook children were studied only after parental consent, and under carefully controlled clinical conditions.

When he learned of Dr. Prince's work with the high-titer gamma globulin, Dr. Krugman borrowed a sample for his experimental work with techniques of passive immunization.

"We felt that we should simulate the situation that occurs when [there is] an accidental inoculation of potentially contaminated blood," he said.

Fifteen children were administered 0.1 ml of a 1:10 solution of untreated serum hepatitis serum. Four hours later, 5 of the 15 children received standard, commercially available gamma globulin. The other ten received the special, high-titer gamma globulin.

Dr. Krugman described the results as "extraordinary findings."

"First, doing serial determinations for the presence of passive antibody following standard gamma globulin, we couldn't detect a thing. But when we tested for passively acquired antibody following the administration, 0.02 ml/pound of body weight, of the special gamma globulin, antibody was detectable as early as three hours after inoculation of gamma globulin, and it persisted for 8 to 29 days."

Three of the five children who received standard gamma globulin had evidence of antigen 43 and 57 days later. Three had evidence of elevated transaminase. This is a very small group, but the attack

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Red Cross tests donated blood for hepatitis

The Red Cross is starting to use a hepatitis screening test on all the blood it collects.

The counter electrophoresis technique will be used, based on a reagent (Hepatitis-Associated Antibody) recently licensed by the Division of Biologies Standards (*JAMA* MEDICAL NEWS 215:1570 [March 8] 1971).

The test, which takes about two hours to complete, is estimated to be 25% to 35% accurate. Sixty blood specimens may be tested at one time with the equipment to be used in the 59 Red Cross regional centers.

In addition, the Red Cross is beginning a nationwide donor registry at its computer center in Alexandria, Va, in an attempt to identify possible hepatitis carriers. In an unusual move, the agency also has authorized its chapters to cooperate in directing volunteer blood donors to non-profit blood banks—even in those areas not covered by Red Cross programs.

The three-part effort is an attempt to increase voluntary blood donations while reducing the incidence of hepatitis, said Tibor J. Greenwalt, MD, Red Cross medical director.

The new donor-recruiting efforts will involve many of the 1,600 Red Cross chapters which are not directly involved in the current Red Cross blood program.

The computerized hepatitis-carrier registry has been developing in the Detroit area since last year. It will be expanded to other areas, eventually becoming a nationwide system, a Red Cross spokesman said. The data will be available to other voluntary blood collection agencies, and the Red Cross, in turn, hopes to add information supplied by these groups.

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matic. One case cited by Dr. Dogo involved a 3-year-old boy with nevus pigmentosus. The cryoprobe was applied at −196 C for four minutes; the therapy was repeated three times after scattered pigmented elements had reappeared. A year later the patient's face showed marked clearing.

Another patient, a 42-year-old man, with spinocellular epithelioma had been treated with diathermal coagulation without appreciable results. The lesion had first appeared about three years earlier and was manifested by moderate ulceration of the lower lip. Liquid nitrogen spray was applied for six minutes on both sides of the lip. Some improvement was noticeable 5 days later, and 40 days later spontaneous healing occurred.

Histological control examinations months later resulted in negative findings as far as neoplastic cells were concerned. ". . . Secondary damage from the destruction of the tissues with liquid nitrogen is clearly inferior to that which would have been caused by surgical removal," commented Dr. Dogo.

"We have some grounds to hope that—once the methodology and application techniques [of cryosurgery] have been improved—low temperatures can become a weapon in association with those already being used in the fight against the most dangerous menace to man's survival."

Hepatitis vaccination may be possible

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rate in such studies is often about 70%, Dr. Krugman said.

"In the ten children who received the special gamma globulin—up to day 78, nothing. As of day 78 (the day of the lecture) there is one who has antigen," said Dr. Krugman. "What will happen next week, or next month, I just don't know. But I think the findings are significant enough to tell us that this is an extraordinary preparation. It deserves intensive study."

The gamma globulin developed by Dr. Prince and associates was derived by standard fractionation techniques, using the pooled plasma of a single hemophiliac donor, Dr. Prince told the assembly. He pointed out that hemophilia patients are repeatedly exposed to serum hepatitis and frequently have extraordinarily high antibody levels.

The gamma globulin in under study at three institutions for retarded children to determine if it will prevent spontaneous contact infections.

"We have also carried out studies on the induction of passive immunity in these children—the antibody levels that can be induced, and how they persist," Dr. Prince said.

"Our preliminary findings indicate that children who receive 0.01 cc/pound of body weight will develop measurable antibody titers. These can be detected with the hemagglutination assay for two to three months."

Two months after administration of this gamma globulin, the children have on the order of 10^{11} antibody molecules per milliliter of blood, he said, adding "this is a considerable degree of potential passive immunity."

This degree of passive immunity might be effective against contact infections involving small numbers of virus particles, Dr. Prince suggested. It might also be effective against some infections acquired from contaminated needles.

"I would question very seriously whether such levels would ever be sufficient to neutralize the quantity of virus present in transfusion. One unit of blood from a carrier of hepatitis virus contains on the order of 10^{15} to 10^{16} virus-like particles."

"The past 25 years have been a frustrating and difficult era for investigators involved in hepatitis research," concluded Dr. Krugman. "The important key which enabled us to open the door with these findings was the discovery of the Australia antigen by Dr. Baruch Blumberg and his associates, and the subsequent contributions by other investigators who devised sensitive tests for the determination of susceptibility and immunity to serum hepatitis."

Alfred Prince, MD, has a warning about the new high-titer gamma globulin developed by his group:

"There is likely to be a demand by clinicians for this product. However, none of this product is available. The (New York) Blood Center has applied for a license to make more of this product and distribute it, but this is a matter before the Division of Biologics Standards. We have none available in physical terms; it has all been allocated to the research studies.

"One must keep in mind also the theoretical possibility that antibody conferred passively may inhibit the primary immune response of the host. Therefore, even though clinical disease may be modified, it is possible that the actual primary of the host may also be modified. The chronic carrier state may be increased in frequency.

"I think, therefore, that these studies must be pursued actively and energetically, but cautiously. The time is certainly not yet present when this material can be recommended for clinical use. But I think it is evident that the eventual goal in all of these studies is the prevention of serum hepatitis. It is now approaching."