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Safety of Immune Serum Globulin with Respect to Homologous Serum Hepatitis.* (20415)

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Immune serum globulin is prepared commercially at the present time by two general processes: (a) salting-out, *e.g.,* by means of ammonium sulphate, and (b) by the cold-ethanol process(1,2) or a variation thereof. Blood obtained either by venipuncture or by extraction from placentas is used as the source material. *The Minimum Requirements of the National Institutes of Health for Immune Serum Globulin*(3) have stipulated that pools consist of at least 500 individual contributions.† In view of the fact that approximately one individual out of 300 receiving blood transfusions may develop hepatitis(4-7), it might be expected that many of the pools of plasma used in the manufacture of immune serum globulin would be infected with the agent(s) of homologous serum hepatitis. General experience indicates that the incidence of homologous serum hepatitis following administration of immune serum globulin must be low. According to Ordman *et al.*(8), one of 400 individuals in one series receiving immune serum globulin developed jaundice. The fact that 74 other children in the series received material from the same lot without untoward sequelae makes it unlikely that the immune serum globulin was the cause of the hepatitis in this one individual. During 1943-44 a follow-up by Janeway of 869 individuals who received immune serum globulin revealed no cases of jaundice(9). Hammon, Coriell, and Stokes, in a follow-up of field studies on poliomyelitis in Utah, found that immune serum globulin injected into 2,800 children was not icterogenic(10). Material prepared by the cold-ethanol method was used in these studies. Cockburn(11) has reported the development of one case of hepatitis among 58 subjects inoculated with immune serum globulin produced by ether fractiona-

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† A recent revision (April 9, 1953) of these Minimum Requirements has increased the figure to 1,000. This is also the figure laid down by the Minimum Requirements for Poliomyelitis Immune Globulin (Apr. 9, 1953).

tion(12). The plasma used in its preparation gave rise to 7 cases of hepatitis among 10 children who were given from 5 to 30 ml parenterally.

Because of the large amounts of immune serum globulin which are being used and because of the small number of reported follow-up studies, it was deemed advisable to determine the infectivity of immune serum globulin with reference to the agent(s) of homologous serum hepatitis by inoculation studies in human volunteers. This was part of an extensive program concerned with the study of the safety of blood and blood products, the general conduct of which is being reported elsewhere(13).

Methods. Material from a single large pool of infected plasma, approximately 130 liters in volume, was used in all of the studies on the safety of plasma and its derivatives. Approximately 16 liters of this plasma were fractionated‡ by the cold-ethanol process, utilizing a combination of Methods 6 and 9 of Cohn *et al.*(1,2). The immune serum globulin so prepared was subjected to the required tests for sterility, safety, and pyrogenicity(3). This material was then inoculated subcutaneously into 10 volunteer subjects, each of whom received 2.0 ml. Simultaneously 5 volunteers in a control group each received 1.0 ml of the original plasma from which the globulin had been produced.

Results. None of the subjects who received globulin developed hepatitis, with or without jaundice, while one of the 5 in the control group developed hepatitis with jaundice having an incubation period of 84 days. A second individual in this control group developed positive hepatic tests suggestive of hepatitis without jaundice.

Additional evidence of the infectivity of the original plasma was provided by the results of a concurrent study designed to determine the infective titer of the plasma. In the course of this, 5 subjects were inoculated with 1.0 ml amounts of a 1/1000 normal saline dilution of plasma from the same vial as that administered to the control group above. All inoculations were performed at the same time. Two cases of hepatitis with jaundice developed in this third group of volunteers. Incubation periods were 89 and 127 days.

Summary. Immune serum globulin produced by the cold-ethanol method from proved infectious plasma failed to produce hepatitis in 10 volunteer subjects inoculated with 2.0 ml each.

‡ Fractionation was carried out by E. R. Squibb & Son.

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