GAMMA GLOBULIN AS A PROPHYLACTIC AND THERAPEUTIC AGENT IN COMMUNICABLE DISEASE*

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A. PLASMA FRACTIONATION

TRANSFUSION of whole blood has long been employed for numerous conditions, such as hemorrhage, anemia, debility, infection, hypoproteinemia, thrombocytopenia, and hemophilia. Blood is a complex mixture of multiple elements with different properties and physiological activities. The desired clinical effect of its transfusion usually depends on the physiological function of a single component. Actually in only one situation, hemorrhage, are all the constituents of blood required to repair the physiologic defect. In most other instances, it would be more rational to employ only that component of blood whose physiological function was desired. Methods for the fractionation of plasma (1) (2) have evolved which permit the chemical isolation of several of its known constituents in a form suitable for clinical use. Thus it not only is more rational to employ these preparations to obtain the desired effect, but it allows the clinician to use larger amounts of the active fraction in order to achieve a more rapid and effective result. It also is obviously more economical to use only the desired fraction and not whole blood, thus leaving the various other fractions to be employed in other patients where their use is specifically indicated by their various physiological requirements.

Following this philosophy, whole blood may be centrifuged, the plasma separated and the red blood cells resuspended in saline to be employed in the treatment of those anemias where the defect is one primarily of insufficient numbers of red blood cells. The use of the pooled plasma which remains is indicated

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primarily in conditions like burns where plasma is lost. It should also be employed for the treatment of prothrombin deficiency or other diseases where the indicated component of plasma has not yet been isolated in a form safe and effective enough for general clinical use. The plasma not so employed may be fractionated to provide the following derivatives:

1. *Albumin.* Although this protein constitutes less than 60 per cent of the total plasma proteins, it is responsible for approximately 80 per cent of the osmotic activity of plasma. The intravenous injection of albumin is indicated in the treatment of shock, hypoproteinemia, and edema (3).
2. *Isohemagglutinins.* These are separated from plasma of group specific bloods and provide powerful and reliable substances for blood grouping (4).
3. *Fibrinogen.* The physical properties of blood clots depend on this protein which can be made into various plastic-like materials. Combined with thrombin, fibrinogen may be converted into clots with various physical properties (5).
4. *Fibrin foam.* These are made up of the same proteins that constitute blood clots and when employed with thrombin offer a substance which is effective as a topical agent for the control of venous bleeding. This has been most widely employed for neurosurgical hemostasis (6).
5. *Fibrin Film.* This is a cellophane-like preparation of fibrinogen plus thrombin which may be used as a dural substitute (7).
6. *Antihemophilic globulin.* This is that fraction of the plasma which has been found to lower the clotting time of patients with hemophilia. This globulin is presumed to be the substance congenitally deficient in the blood of such patients.
7. *Gamma globulin.* This will be discussed in greater detail below.

B. Normal Human Serum Gamma Globulin

Concentrated normal human serum gamma globulin is that fraction of normal human plasma which contains the immune bodies usually present against infectious disease. Early in the course of the plasma fractionation program, it was appreciated that this protein might be of practical value in the control of

various diseases (8). The methods currently employed recover and concentrate about 75 per cent of gamma globulin in a purity of 95 per cent or better. Gamma globulin so prepared contains antibodies present in approximately twenty-five fold concentration over that found in the plasma from which it was derived (9). Thus, each 10.0 cc. of this material contains the antibody equivalent of approximately 250 cc. of pooled adult plasma or most of the immune bodies present in 500 cc. of whole blood. The preparations tested show a fairly constant titre of antibodies to the more common diseases present in the adult donor population. This may well be expected to vary somewhat from continent to continent or as the incidence of certain diseases may vary with a given group of adult donors. Accordingly, preparations containing unusually high titres of specific antibodies may be derived from the plasma of hyperimmune or convalescent patients. The gamma globulin derived from the fractionation of pooled normal adult plasma in the United States was soon demonstrated to be effective as a safe and reliable agent in the prophylaxis of measles (10) (11).

Physical Properties, Administration and Reactions

Gamma globulin is prepared as a clear, colorless, viscid solution, which is stable for long periods of time. The present material may produce serious reactions if injected intravenously and it should therefore always be given by the intramuscular route. When so administered in the usual dosage, reactions occur in 1 to 2 per cent of the cases (12). About 0.2 per cent of inoculated patients experience general reactions such as headache or significant malaise. Significant local reactions in the nature of pain, redness and swelling are seen in 0.6 per cent and febrile reactions in 0.4 per cent. The use of gamma globulin has not resulted in the production of serum jaundice.

Clinical Use

I. MEASLES

A. Prophylaxis. If gamma globulin is given in doses of 0.1 cc.

per pound of body weight within the first six days after exposure to measles, the disease will be prevented in at least 80 per cent of exposed, susceptible contacts and modified in practically all the remaining contacts. The passive immunity achieved in this fashion will last for at least three weeks. If re-exposure occurs after this period of time, another similar inoculation should be given if prevention is still desirable. Measles should be prevented when exposure occurs in: (1) Infants younger than six months whose mothers are not immune; (2) infants between the age of six months and three years; (3) children who are debilitated or ill with another disease; (4) patients with pulmonary tuberculosis; (5) patients on hospital wards who, if allowed to have measles, might expose other sick patients; (6) children in whom the presence of measles would disturb the surrounding social environment to an unusual degree and (7) non-immune pregnant women, especially if exposed during the first trimester.

If gamma globulin is given in doses of 0.02–0.025 cc. per pound of body weight within the first eight days after exposure to measles, the disease will be modified in most of the exposed susceptible patients and prevented in relatively few. Although failure to achieve mild measles occurs in a small percentage of patients who develop the unmodified disease, gamma globulin appears to be the safest, most convenient, and effective agent now available. Comparison shows gamma globulin to be at least as effective and easier to use than the less easily available convalescent serum (13). Placental extract is less reliable for modification as well as for prevention of measles and results in a significantly greater incidence of both general and local reactions (14).

There is no absolute proof to date that this scheme of "active immunization" produces a lasting immunity, although most of the evidence on hand indicates that this is probably true in the vast majority of instances. It would, therefore, seem indicated to attempt to modify the disease in all children over the age of three years except for those exceptions listed above, which con-

stitute the various indications for prevention of the disease. Such a scheme permits the acquisition of permanent immunity while having a mild disease. If the disease is prevented, the individual may well have a future unrecognized exposure followed by severe unmodified measles. Another cogent argument in favor of attempted modification is that the measles complication rate has been ten times as high in the unmodified as in the modified variety with no fatal complications seen to date in the latter group (12).

Because of the variability of modified measles, the patient in whom this condition is anticipated must be observed carefully throughout the incubation period so that unusually mild forms are not overlooked. The classical findings of cough, coryza, conjunctivitis, Koplik spots, fever, malaise, and rash are usually present in varying degrees. Any of these cardinal symptoms may exist alone or in conjunction with any or all of the others. The incubation period is often prolonged to twenty-one days, although the average time is approximately fourteen days. In most cases, there is a moderately mild mobilliform rash which lasts a shorter period of time than that seen with average measles. In a small number of patients with mild measles, the rash may be absent. The respiratory symptoms which constitute such a striking and annoying part of average measles are usually mild and may often be absent. The temperature is rarely elevated beyond 103° and usually ranges between 100–102°, with little associated malaise or prostration.

B. Treatment. There is some evidence that the administration of gamma globulin in large doses (*i.e.* 15–30 cc.) during the pre-eruptive stage of measles may result in a partially attenuated form of the disease (15). The results are not yet well enough defined to merit using the material in the routine treatment of measles.

II. INFECTIOUS HEPATITIS

Several well controlled studies have established the fact that if gamma globulin is given in doses of 0.1 cc. per pound of body weight early in the incubation period of infectious hepatitis, a

very definite reduction in the case incidence of this disease will occur in intimately exposed individuals (16) (17) (18). The protection afforded by this procedure would not appear to indicate its general use in the vast majority of the casually exposed civilian population in view of the extremely low rate of cross infection. It would appear more rational to reserve the use of gamma globulin to attempt to prevent the disease when exposure occurs in (1) military personnel living in close contact with each other, (2) institutions where intimate exposures are considerable, (3) patients who suffer from some serious debilitating disease, and (4) pregnant women.

If gamma globulin is given in doses of 0.3 cc. per pound of body weight early in the course of infectious hepatitis, no apparent modification of the disease ensues (19).

The value of gamma globulin in the prevention of attenuation of homologous serum jaundice is not yet well defined (20).

III. MUMPS

Gamma globulin processed from the plasma of patients convalescing from mumps has been shown to decrease the incidence of orchitis in adult males significantly when given in doses of 20 cc. at the onset of the disease (21). Material prepared from normal adult plasma pools is without value in the prevention of mumps or of orchitis.

IV. PERTUSSIS

Gamma globulin processed from pooled hyperimmune pertussis serum is of definite value in passive immunization against whooping cough. This material is also of value in the treatment of pertussis, especially if therapy is instituted early in the course of the disease. Normal gamma globulin is again without apparent value.

V. POLIOMYELITIS

Gamma globulin has been used in unusually high doses for the treatment of preparalytic poliomyelitis without any apparent benefit (22). There is no clinical evidence that gamma globulin is of value in the prevention of poliomyelitis, although

there is evidence that human immune bodies may aid in preventing experimental transmission of the virus to laboratory animals (23).

VI. SCARLET FEVER

Studies are now being carried out to determine the value of both normal and convalescent gamma globulin in the prophylaxis and treatment of this disease. It appears likely that they may be of some value.

VII. GERMAN MEASLES

The possible use of gamma globulin in the prevention and treatment of this disease is under study.

VIII. CHICKEN POX

Normal gamma globulin is ineffective in the prevention of chicken pox and its role in treatment is unknown.

IX. INFANTILE DIARRHEA

The evidence to date indicates that gamma globulin is of no value in the prophylaxis and treatment of infantile diarrhea (24).

Summary

Gamma globulin is that fraction of the plasma proteins which contains the immune bodies. Recent preparations of this material contain antibodies which are concentrated approximately twenty-five fold over the pooled plasma from which they are derived.

When given intramuscularly, it has proved to be a particularly effective and safe agent for the prevention and modification of measles. Gamma globulin is also capable of preventing or modifying infectious hepatitis in a large proportion of exposed individuals. Its role with regard to prophylaxis of homologous serum jaundice, mumps, scarlet fever, pertussis, poliomyelitis, and other infectious diseases is now being studied. Therapeutically, it may prove of value in the treatment of scarlet fever, pertussis, and very early measles. Gamma globulin from convalescent plasma has proved useful in reducing the incidence of orchitis in mumps.

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