

Cutaneous and Systemic Reactions to Human Plasma

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A BLOOD transfusion is as much an organ transplant as is a skin graft, although it is not usually considered as such. It would be of great interest and considerable practical significance to know whether blood plasma is capable of provoking a homograft response when transplanted to a member of the same species. The purpose of this study was to determine whether or not human plasma proteins possess the same properties of immunologic individuality which characterize skin and other tissue proteins.

It is well known that the iso-antigens associated with erythrocytes are of significance in the causation of transfusion reactions, and recently it has been suggested that leukocyte antibodies may be responsible for some allergic reactions to transfused blood.¹ It is generally assumed, however, that human plasma is nonantigenic for human recipients, in spite of several sporadic published reports of allergic reactions to transfused plasma.²⁻⁸ Such reactions have been attributed to either the passive transfer of antibodies or the inadvertent administration of proteins to which the patient was already sensitive. Dameshek and Neber⁹ found evidence for a plasma factor in allergic reactions to whole blood occurring in patients with various hematologic disorders. They advised the use of washed erythrocytes as a means of preventing these reactions. Whealing in human skin as a result of intradermally injected human plasma was reported by Levine and State.¹⁰ These workers believed that the whealing reaction was due to major blood group incompatibility, but they did suggest that plasma factors may account for some allergic transfusion reactions. Maunsell⁶ observed that when pooled human serum, dried and reconstituted, was transfused into atopic persons, urticaria occurred in 80 per cent, whereas nonatopic recipients gave no reaction.

In previous publications, Bliss and his co-workers^{11, 12} reported on plasma incompatibility in dogs. They skin-tested dogs with the dog's own plasma and with plasma from several other dogs. (In this article, plasma from the recipient itself will be called autologous plasma, and plasma from a different individual of the same species will be called nonautologous plasma.) At the same time as the animals were skin-tested with autologous and nonautologous plasma,

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Read before the annual meeting of the American Academy of Allergy in Chicago, Illinois, Feb. 9, 1959.

Received for publication May 19, 1959.

they were given an intravenous injection of Evans blue dye. (The dye is bound to the plasma proteins, and the degree of extravasation of dye into the skin at the site of injection serves as an index of capillary permeability.) A total of 350 plasmas were tested in 180 dogs. In no case was there any reaction to autologous plasma, but when nonautologous plasma was used a blued area of increased capillary permeability always appeared at the site of injection of nonautologous plasma. The same distinction between autologous and nonautologous plasma was easily demonstrated among purebred and inbred dogs and was found to be unrelated to canine erythrocyte types.¹³

Bliss and associates also found that in dogs rapid transfusion of non-autologous plasma from a single donor nearly always resulted in the development of urticaria in the recipient animals. No reactions occurred in dogs receiving similar transfusions of autologous plasma. There was considerable evidence to show that in dogs both the cutaneous and the systemic reactions to nonautologous plasma were due to histamine release.

The present investigation was designed to explore the possibility that similar manifestations of plasma incompatibility may occur in human beings.

METHODS AND MATERIALS

Subjects.—The subjects were all healthy men between the ages of 20 and 35 years. Persons whose skin showed a positive intracutaneous reaction to saline, as well as those who showed no reaction to histamine, were rejected as subjects. The incidence of clinical allergy among the subjects was about 10 per cent, which is approximately that of the general population.

Skin Testing.—Fresh heparinized plasma (0.75 mg. heparin per 10 ml. of whole blood), 0.1 ml., was injected intradermally through a 26 gauge needle at each site in the recipient's back. At the time the sites were placed, 100 mg. of Coomassie blue dye (Ayerst, McKenna & Harrison, Montreal) was injected intravenously into the recipient. The skin tests were made in duplicate and were read in thirty minutes by two observers. An area of blueing, 2 to 3 mm. in diameter, appeared in each site at the point of needle puncture. Any larger area of blueing was considered to constitute a positive test, and the diameter was recorded in millimeters. The intensity of color and the presence or absence of flare formation were also noted.

Collection of Plasma.—Donors were bled into sterile siliconized vacuum bottles containing 0.55 gram citric acid and 1.54 grams trisodium citrate in 30 ml. of distilled water. Approximately 500 ml. of blood were collected from each donor. The blood was centrifuged at 10° C. at 1,700 r.p.m. and then the plasma was removed by suction and transferred to sterile bottles for storage. The plasma was stored at -20° C. for one week before it was used.

Transfusion of Plasma.—The plasma was infused through a No. 90 polyethylene catheter inserted in the antecubital vein; 500 ml. was given over a period of thirty minutes. A Sigmamotor pump was used to ensure a uniform rate of administration.

Determination of Blood Volume.—Radioactive iodinated serum albumin (RISA), 10 μ c., was given intravenously for each blood volume determination. Plasma samples were taken at five-minute intervals for twenty minutes following the injection of RISA. The degree of radioactivity in each sample was determined in a well type of scintillation counter, and the blood volume was calculated from the values thus obtained.¹⁴

EXPERIMENTS AND RESULTS

Cutaneous Reactions.—The plasmas of forty-seven donors were tested in the skin of twenty-three recipients. Each recipient was skin-tested with autologous plasma and one or more nonautologous plasmas. In every case the donor and recipient were of the same ABO and Rh blood types. It was found that if no intravenous dye were given it was difficult to distinguish between the blebs produced by autologous and nonautologous plasma. A flare surrounded some of the nonautologous blebs, but this was not found to be a reliable means of separation. On the other hand, when dye was administered, a clear-cut differentiation was possible in almost every case. Although a bleb of almost identical size was produced at both the autologous and the nonautologous sites, there was marked blueing of the nonautologous blebs. There was no blueing at the sites of injection of autologous plasma.

TABLE I. COMPARATIVE DIAMETERS OF BLUED AREAS IN PAIRED SKIN TESTS WITH HUMAN PLASMA

	NO. OF CASES	PER CENT
Autologous greater than nonautologous	0	0
Autologous equal to nonautologous	9	19
Autologous less than nonautologous	38	81
	47	100

A difference of more than 4 mm. in diameter between the blued areas produced by autologous and nonautologous plasma in the same recipient was considered to be significant. Such a difference is easily distinguished on visual inspection without measurement.

TABLE II. THE REACTION OF HUMAN SKIN TO INTRADERMAL HUMAN PLASMA

PLASMA	NUMBER OF TESTS	AVERAGE DIAMETER OF BLUED AREA (MM.)	STANDARD DEVIATION (MM.)
Autologous	23	2.9	0.3
Nonautologous	47	9.1	3.5

The results of skin testing with autologous and nonautologous plasma are summarized in Tables I and II. In 81 per cent of the cases the skin reaction to nonautologous plasma was clearly greater than the reaction to autologous plasma, while in 19 per cent of cases the blued areas were of approximately the same size. In no case was autologous plasma more reactive than nonautologous plasma. In all the cases where there was not a clear distinction between autologous and nonautologous plasma, there was a reduced response to intradermal histamine, which meant that the recipients had poorly reactive skin.

When the average diameters of the blued areas were compared, it was found that the average area of increased capillary permeability produced by autologous plasma was 2.9 ± 0.3 mm., whereas that produced by nonautologous plasma was 9.1 ± 3.5 mm. (Table II).

Systemic Reactions.—In order to explore the possibility that this cutaneous sensitivity to nonautologous plasma might be of importance in the production of transfusion reactions, six healthy young men were given a transfusion of 500 ml. of their ~~own plasma, which had been~~ removed on a previous occasion. In no case did any untoward reaction to autologous plasma occur. The same subjects were then grouped into three pairs, and each subject was given 500 ml. of plasma taken from the other member of the pair. In three of these six nonautologous transfusions, there were severe reactions (Table III). It should be emphasized that 500 ml. of plasma was given over a period of thirty minutes. This represents a larger quantity of plasma given at a more rapid rate than is customary in normal hospital practice. The recipients were also given an intravenous injection of Coomassie blue dye to accentuate the skin reactions which were tested at the same time. Control studies showed that the transfusion reactions were not caused by the dye.

TABLE III. ALLERGIC REACTIONS TO TRANSFUSED PLASMA IN PAIRED HUMAN SUBJECTS

	PAIR I (A+)		PAIR II (O+)		PAIR III (O+)	
Plasma donor	1	2	3	4	5	6
Plasma recipient	2	1	4	3	6	5
Diameter of recipient's skin reaction to recipient's plasma	3 mm.	3 mm.	5 mm.	4 mm.	3 mm.	2 mm.
Diameter of recipient's skin reaction to donor's plasma	10 mm.	9 mm.	15 mm.	9 mm.	3 mm.	12 mm.
Allergic reaction	+++	-	++++	-	+++	-
History of allergy in recipient	Yes	No	Yes	Yes	No	No

One reaction to nonautologous plasma will be described in detail. The subject, a healthy 27-year-old resident physician with a history of seasonal rhinitis, began to complain of itching and swelling of the upper lip twenty minutes after the beginning of the infusion of nonautologous plasma. There was no visible change in the skin except for a faint erythema in the flexural creases of the neck and axillae. Multiple urticarial wheals then appeared over the entire body. The regions of urticaria were stained blue by the dye which had extravasated from the capillaries. Sixty minutes after the beginning of the transfusion, the wheals about the face had become confluent and appeared as diffuse blue areas which were slightly raised and surrounded by a patchy erythema. There was similar involvement of the anterior chest wall and back. The subject at this stage complained of intolerable itchiness, chills, nasal blockage, and a feeling of stiffness of the face. His symptoms disappeared gradually following the administration of 50 mg. of diphenhydramine intramuscularly and 0.5 ml. of epinephrine 1:1,000 subcutaneously. Ten hours later, the angioedema of the face recurred and was accompanied in this instance by pain in the knees and ankles. Diphenhydramine and epinephrine again produced a gradual remission of symptoms.

The transfusion reactions in the other subjects were essentially similar, except that joint pain occurred only in the subject already described. Six additional subjects were given rapid infusions of 500 ml. quantities of plasmas pooled from three donors. This, of course, is a much smaller pool than is usual for pooled plasma. Four of these six recipients had allergic transfusion reactions of varying degrees of severity.

The total experience with the transfusion of autologous and nonautologous plasma is summarized in Table IV. In six autologous transfusions given under the conditions already described, there were no adverse reactions, whereas there were seven transfusion reactions in twelve nonautologous transfusions.

TABLE IV. ALLERGIC REACTIONS TO TRANSFUSED PLASMA

PLASMA	NUMBER OF TRANSFUSIONS	NUMBER OF REACTIONS	REACTION RATE (PER CENT)
Autologous	6	0	0
Nonautologous	12	7	58

The skin tests proved to be of no value in predicting which subjects would have reactions and which would not. There was no correlation between the size of the skin reaction to nonautologous plasma and the severity of the systemic reaction to the infusion of that plasma.

Blood Volumes.—Blood volumes were determined in each subject before and after the transfusion of plasma. It was found that in those persons who had transfusion reactions, the expected increase in blood volume did not occur, presumably due to leakage of fluid from the capillaries. In some cases there was even a net decrease in blood volume. Detailed results of the blood volume studies will be reported at a later date.

DISCUSSION

On the basis of these experiments, it would appear that, in human beings, the normally responsive skin of every individual will react to the plasma of every other individual but not to his own. The plasma antigens are thus somewhat different from the naturally occurring cellular antigens of the blood, in that no equivalent to the blood types has yet been discovered. Each person appears to possess his own distinctive pattern of plasma antigenicity. In this respect, the plasma antigens most resemble the antigens found in tissue transplantation studies. However, they differ from tissue antigens in their capacity to elicit an immediate type of reaction in contrast to the delayed type of response provoked by homografts.

Plasma antigens may account for some of the reactions occurring in otherwise compatible blood transfusions. If this hypothesis is correct, allergic reactions should occasionally occur with plasma transfusions. In a series of 10,000 infusions of pooled plasma reported by Miller and Tisdall,⁸ there were allergic reactions in 1.05 per cent. Weinstein¹⁵ reported an allergic reaction rate of 1 per cent in 1,500 transfusions of unpooled plasma. In our series, the allergic reaction rate was approximately 50 per cent. The high incidence of

reactions in our study is probably accounted for by the fact that large quantities of plasma were given rapidly. Thus, any tendency for allergic reactions to occur was accentuated by the method of administration.

In the past, reactions to plasma have been assumed to be due to the passive transfer of skin-sensitizing antibodies, or to allergens to which the recipient was already sensitive. This explanation would not seem to be valid in our cases, since the incidence of systemic reactions approached 50 per cent. It is most improbable that 50 per cent of the population is sufficiently sensitized to food or other allergens for urticaria to be produced in such a manner. The incidence of systemic reactions to nonautologous plasma was not higher in allergic persons. In fact, in the majority of cases in which systemic reactions occurred, there was no history of allergy in either the donor or the recipient.

The urticaria and failure of plasma expansion associated with the administration of nonautologous plasma are probably best accounted for by increased capillary permeability similar to that demonstrated on skin testing. The infused fluid presumably leaks from the blood vessels into the skin and tissue spaces. Animal experiments strongly suggest that the increase in capillary permeability caused by nonautologous plasma is due to the release of free histamine.¹² It is probable that a similar mechanism exists in human beings, but this hypothesis has yet to be proved.

In the treatment of shock and severe hemorrhage, blood or blood plasma may have to be administered rapidly. This use of blood is especially important in times of national emergency. As a result of this study, it would seem reasonable to assume that patients who have allergic reactions to rapidly administered plasma derive little or no benefit from the transfusion. It is possible that under these circumstances a blood substitute, such as dextran, might be both more effective and easier to use. It would also appear that, contrary to current surgical teaching, there may be considerable advantage in slowing down the rate of transfusion in those patients who are to receive large quantities of whole blood or blood plasma.

SUMMARY

1. The normally responsive skin of every person will react to the intradermal injection of plasma from every other person with a localized area of increased capillary permeability. There is no reaction to the recipient's own plasma.
2. Allergic reactions occur in approximately 50 per cent of persons given rapid transfusions of unpooled plasma taken from other persons. No reactions occur when the recipient receives his own plasma.

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