IMMUNODEPRESSIVE PROPERTIES OF ANTILYMPHOCYTIC SERA

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Antithymocytic (ATS) and antilymphocytic (ALS) sera obtained from immunized guinea pigs were injected into rabbits with skin heterografts. The time of survival of the skin heterografts was increased only if the sera were injected subcutaneously, but not intravenously, before and after transplantation or in large doses after transplantation. Suppression of transplantation immunity was obtained not only after a first, but also after a second transplantation. In one case, when ALS was used, permanent tolerance to the heterograft was achieved. ALS and ATS produced different effects if injected by the same scheme in equal doses.

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It was shown in 1963 [12] that injection of heterologous antilymphocytic (ALS) serum into rats resulted in longer survival of a skin heterograft. Depression of transplantation immunity by means of ALS was later observed in experiments on mice, rats, and dogs after transplantation both of the kidney and of the skin [3, 4, 6-10]. ALS has also been used successfully in clinical practice during kidney transplantation [11]. Most workers now consider that ALS is one of the most promising preparations which can be used to suppress heterograft rejection reactions.

The immunodepressive properties of ALS were studied in the present investigation in rabbits receiving skin heterografts.

EXPERIMENTAL METHOD

ALS and antithymocytic serum (ATS) were obtained by double immunization of guinea pigs with a suspension of living spleen or thymus cells from rabbits. The dose of cells per intraperitoneal injection was 100-150 million. Serological characteristics of the antisera were determined by the tests previously described [1]. Heterotransplantation of a skin graft measuring 3 × 3 cm was performed on the rabbit's ear or back.

EXPERIMENTAL RESULTS

Tests showed that the ALS contained lymphocytotoxins and antibodies agglutinating lymphocytes in titers of 1 : 125 and 1 : 64 respectively. No leukocytic antibodies against spleen cells were found in the ATS.

When injected intravenously, ALS caused marked edema and inflammation at the root of the ear (ALS was injected into the auricular vein).

Inhibition of the general condition of the animals and absence of delay in rejection of the heterografts after injection of ALS in a dose of 0.5 ml (5 times before and 4 times after transplantation at intervals of 1 day) led us to discontinue intravenous injection of the preparation in subsequent experiments, and to inject ALS and ATS subcutaneously only.

Subcutaneous injection of ALS before and after transplantation caused no local inflammation, and in some rabbits considerably increased the periods of survival of the heterografts (Table 1).

In one case (period of observation 2 years) permanent survival of the donor's skin was obtained (Fig. 1). Injection of small doses of ALS only before or only after transplantation proved ineffective. On the other hand, ATS prolonged survival of the heterografts only if injected in large doses after transplanta-

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TABLE 1. Results of Heterotransplantation of Skin in Rabbits Receiving ALS or ATS Subcutaneously

Serum	Scheme of injection of serum	Dose of injection (in ml)	No. of observations	No. of rabbits in which graft survived for			
				2	3	4	5 weeks and more
–	–	–	10	0			
ALS	5 times before transplantation at intervals of 1 day	0.5	5	0			
ALS	5 times after transplantation at intervals of 1 day	0.5	5	5	1	1	0
ALS	5 times before and 5 times after transplantation at intervals of 1 day	0.5	11	9	5	3	2
ALS	Twice on the 2nd and 5th day after transplantation	10	6	0			
ATS	5 times before and 5 times after transplantation on alternate days	1	4	0			
ATS	Twice on the 2nd and 5th day after transplantation	10	6	6	4	1	1

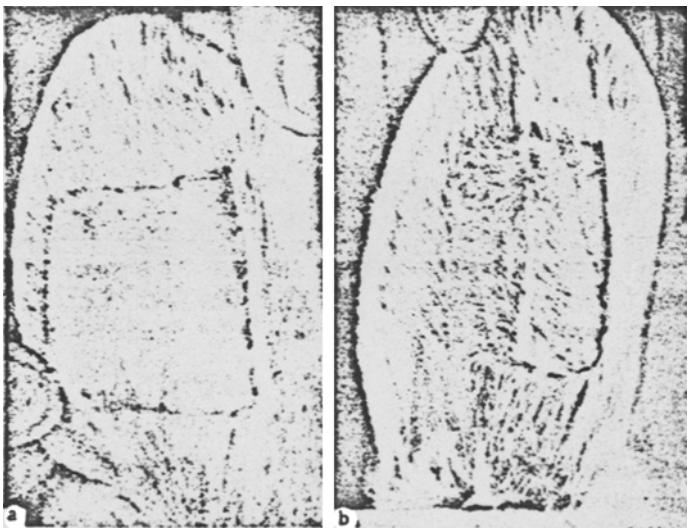

Fig. 1. Skin heterograft on a rabbit receiving ALS. Photographs taken 1 (a) and 20 (b) months after transplantation.

tion (by Medawar's method [6, 7]). Slower injection not only of the first, but also of second and third grafts transplanted from the original donor at intervals of 3-4 weeks, was observed in these experiments (Table 2).

It is interesting to note that rapid rejection of the second and third grafts did not take place in those cases when prolonged survival of the first heterograft could not be obtained with the aid of ATS.

Three main hypotheses have so far been suggested to explain the mechanism of the immunodepressive action of ALS: 1) the serum has a direct lymphocytotoxic action [4, 9, 10]; 2) the serum produces an afferent block, preventing the lymphocytes from recognizing the antigen or causing their nonspecific transformation [6, 7]; 3) the serum produces an efferent block, interacting mainly by local application with antigenic determinants of the graft [1, 2, 5].

Considering that in our experiments ALS and ATS differed in their serologic properties and gave different effects in vivo, it can be assumed that ALS and ATS are different biological substances, and that separate optimal schemes of administration must be worked out for each of them. The immunodepressive effect of antilymphocytic sera is evidently not entirely the result of their lymphocytotoxic action. It may

TABLE 2. Results of Repeated Heterotransplantation of Skin in Rabbits Receiving ATS

Rabbit No.	Periods of survival of heterografts (in days)		
	1st	2nd	3rd
816	48	18	14
428	26	21	12
641	14	21	12
854	14	21	11

be postulated that both ATS and ALS are capable of suppressing manifestations of immunologic reactions at different levels, and the theories of both afferent and efferent blocking may both be productive in explaining their action, depending on the preparation used and the scheme of its administration.

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