ACTION OF ANTI-PITUITARY SERUM ON ALLOGENEIC CARDIAC TRANSPLANT REJECTION IN RATS

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Anti-pituitary serum (APS), injected into rats of the August strain, prolongs the life of an allogeneic transplant (the heart of newborn Wistar rats). After injection of APS the animals showed inhibition of growth and involution of the thymus of varied intensity. In these animals the electrical activity of the transplant was more marked and lasted longer (from 14 to 37 days) than in the control group (from 9 to 30 days). The pathogenetic mechanisms of the action of APS are probably connected with the inhibition of pituitary function cessation or diminution of somatotropic hormone secretion).

The theory of neuro-hormonal regulation of immunity was formulated by Zdrodovskii as a special case of a protective-adaptive reaction of the body [3]. The experimental basis of this theory was established by Gurvich [1, 2] using a model of antibody synthesis. A previous investigation [4] showed that the blocking of anabolic processes by anti-pituitary and anti-somatotropic sera causes a decrease in the primary immune response.

It was decided to make an experimental study of the neuro-hormonal regulation of transplantation immunity with special reference to inhibition of the anabolic components of regulation on the transplant rejection reaction.

TABLE 1. Duration of Maintenance of Electrical Activity of Transplanted Heart in Experimental and Control Group

Day of experiment	Number of transplants with positive ECG			
	control		experiment	
	abs.	%	abs.	%
9	53	100	37	100
14	35	66,5	37	100
16	24	44,9	31	83,7
18	12	22	20	54
21	6	11,6	14	37
24	4	7,6	8	21
26	3	5,7	6	16,2
30	1	1,9	5	13,5
35	0	0	4	10,8
37	0	0	1	2,7
39	0	0	0	0

EXPERIMENTAL METHOD

To inhibit anabolic reactions an anti-pituitary serum (APS) obtained from rabbits immunized with homogenates of the pituitary glands from 30 to 40 rats was used. The homogenates were injected either intravenously for 3 days or, in Freund's adjuvant into the popliteal lymph glands, followed by subcutaneous revaccination one month later. Serum which, if injected once or twice into 20-day rats, caused involution of the thymus was used in the work. The model of heterotopic allogeneic transplantation of the heart used in the investigation enabled the state of the graft to be assessed both functionally and morphologically.

Experiments were carried out on August and Wistar rats. The donors of the heart were newborn (1-2 days) Wistar rats and the recipients were August rats weighing 30-50 g. Transplantation was carried out by Fulmer's method [6]. The transplant (a whole heart or half of a heart after sagittal section) was placed in a pouch of skin from the dorsal surface of the ear.

The batch of animals with transplanted hearts was divided into two groups (experimental and control). The animals of the experimental group

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TABLE 2. Duration of Function of Transplanted Heart (in days)

	Control	Experiment
Number of observations	53	37
Arithmetic mean	15	20,7
Median	14	18
Confidence limits of median with probability of 99%	13—16	17—23

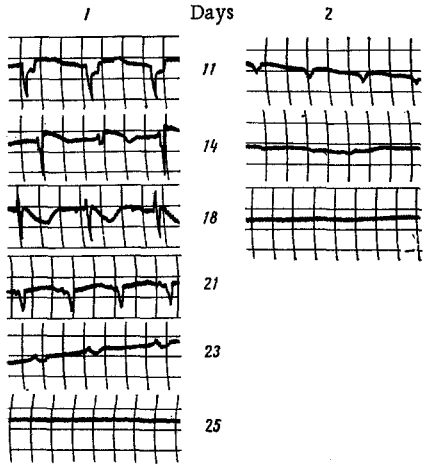

Fig. 1. Electrical activity of transplant in experimental (1) and control (2) series. Halves of the same heart were transplanted into the experimental and control rats.

received intraperitoneal injections of 1 ml APS 24 h after the operation and thereafter at intervals of 1-2 days. If the preparation was poorly tolerated by individual rats, the next routine injection of serum was withheld. The serum was injected from 7 to 14 times (until loss of the contractile function of the transplant). Rats of the control group received injections of physiological saline or normal rabbit serum. Survival of the transplant was judged from its electrical activity, which was recorded at intervals of 1-2 days by the ÉKPSChT-4 electrocardiograph starting from the 7th-9th day.

Altogether 90 transplantations were performed: the whole heart in 19 cases and a half a heart in 71 cases. In some experiments one half of the heart was grafted into the experimental and the other half into the control animals. In the overwhelming majority of animals the transplant survived well. Animals in which electrical activity of the transplant was absent on the 7th-9th day were excluded from the experiment.

EXPERIMENTAL RESULTS

The duration of function of the transplant in the control group varied from 9 to 30 days. Electrical activity of the whole transplant and of the half-heart was almost identical. In most cases the electrical activity of the transplant did not last longer than 16 days (Table 1).

In the experimental groups of animals inhibition of growth, a varied degree of intensity of involution of the fibers, and diarrhea were observed after the injection of APS. In these animals the electrical activity of the transplant was more marked (Fig. 1) and could be detected longer (from 14 to 37 days) than in the control group (Table 1). On the 14th day in the experimental group, for instance, contractions of the myocardium were recorded in 100%, and in the control group in 66% of cases, while on the 18th day in the experimental group they were recorded in 54% and in the control group in 22% of cases.

To assess possible individual variations in immunological incompatibility between the tissues of the Wistar and August rats, in some cases half of the heart was transplanted into the experimental and the other half into the control animal. Of the 16 transplanted halves of the heart in the experimental group a distinct lengthening of myocardial function compared with the control was observed in 13 transplants: 2, 4, 5, 5, 5, 7, 7, 7, 7, 8, 10, 12, 15 days. In 3 cases the graft functioned longer (by 2, 3, and 4 days) in the control.

Statistical analysis of the material by calculation of the median for 99% probability shows that the differences between the experimental and control series are significant (Table 2).

In 30 cases the action of APS on rejection of the allogeneic transplant was investigated histologically. The thymus, spleen, and transplant with the surrounding tissues of the ear from the experimental and control animals were studied histologically 3-7 days after the transplant had lost its electrical activity.

Five injections of APS into rats caused involution of the thymus of varied intensity with partial or complete disappearance of thymocytes from its cortex (Fig. 2a). Lympholysis and inhibition of hematopoiesis were observed to a lesser degree in the spleen. Later the structure of the thymus was restored and only slight depopulation of the cortex could be observed in some of the autopsied animals.

In the control and experimental animals, after the transplant had ceased to function, the typical reaction of rejection of the transplant with necrosis of the myocardial muscle fibers, their partial or complete replacement by connective tissue (Fig. 2b), and marked lymphoid infiltration of the surrounding connective tissue (Fig. 2c) and, sometimes, of the transplant itself (Fig. 2d) was observed. Complete correlation was

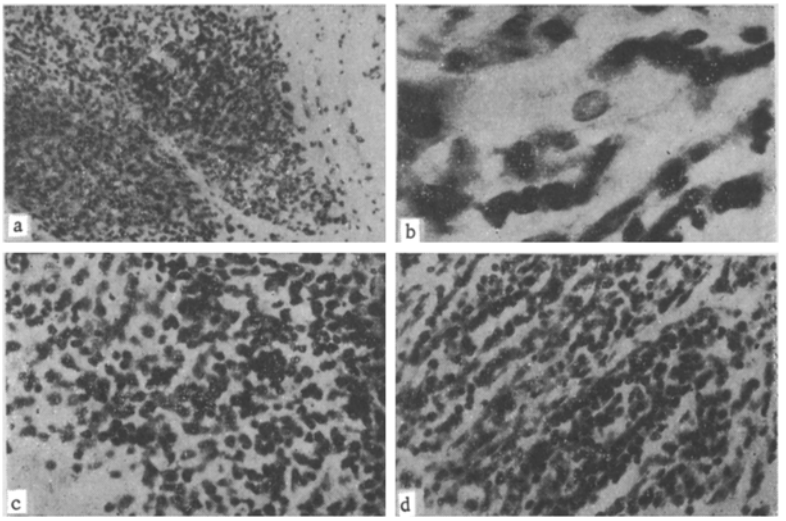

Fig. 2. Morphological picture of thymus and transplant in experimental rats: a) disappearance of thymocytes from cortex of thymus after injection of APS (stained with hematoxylin-eosin, 90×); b) replacement of myocardium of transplant by connective tissue. Single muscle fibers with cross-striation preserved (600×); c) lymphoid infiltration of connective tissue around transplant 5 days after loss of electrical activity of allogeneic heart transplant; d) lymphoid infiltration of intrinsic connective tissue of transplant in a rat receiving APS (200×).

established between the loss of functional activity by the transplant and the development of the rejection reaction.

Injection of APS into the experimental animals prolonged the period of function of the transplant, thereby indicating a definite but brief inhibition of transplantation immunity. The pathogenetic mechanisms of action of APS, as the histological findings suggest, consist of sharp suppression of the function of the adenohypophysis with cessation or diminution of the secretion of the corresponding hormones, especially somatotropic hormone. As a result a picture of the well-marked action of the antiphlogistic hormones, inducing lymphatic processes and delaying the development of transplantation immunity and antibody synthesis, is produced. For instance, inhibition of immunological processes has been observed after hypophysectomy [5, 7] and during the action of APS and antisomatotropic serum [4, 8]. Inhibition of immunogenesis in response to action exerted on the pituitary has been shown to be obtained more easily if homeostasis is disturbed [5] or in young animals [4, 8].

Activation of corticoids and cortisones in the later stages during prolonged administration of APS is followed by restoration of the normal hormonal background through adaptive mechanisms or immune responses of the body against the foreign serum.

Blocking the anabolic components of neuro-hormonal regulation thus leads not only to a decrease in antibody synthesis, but also to the inhibition of transplantation immunity. These results are of definite theoretical interest, for they confirm P. F. Zdrodovskii's theory of the neuro-hormonal regulation of immunological processes.

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