

## EXPERIMENTAL BIOLOGY

### THIO-TEPA AND THIO-TEPA PLUS HYDROCORTISONE IN PROLONGING VIABILITY OF HOMOGRAFTS

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A morphological study of thyroid homografts in rabbits and kidney homografts in dogs has shown that rejection of the graft, whether on a vascular pedicle (kidney) or not (thyroid), follows qualitatively the same course. Administration of thio-TEPA to the rabbits prolonged survival of the homografts from 16 to 25 days. Administration of thio-TEPA with hydrocortisone in the experiments on dogs delayed rejection of the grafted kidney until 14-16 days compared with 8-10 days in the control.

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The value of cytostatic drugs in suppressing the protective response of the recipient during organ homografting has recently been demonstrated [3, 4].

The object of the present investigation was to study the effect of one compound of this group - thio-phosphamide - on viability of thyroid and kidney grafts.

#### EXPERIMENTAL METHOD

The efficacy of thio-TEPA was studied in experiments on thyroidectomized rabbits with an autografted or homografted thyroid and on dogs with a homografted kidney. The technique of intraocular transplantation

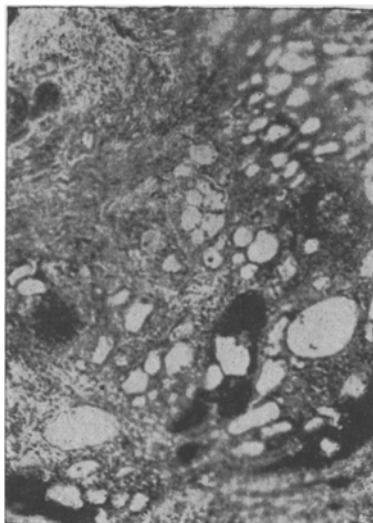


Fig. 1

Fig. 1. Massive round-cell infiltration of thyroid homograft in rabbit 10 days after operation. Control group. Hematoxylin-eosin, 80 $\times$ .

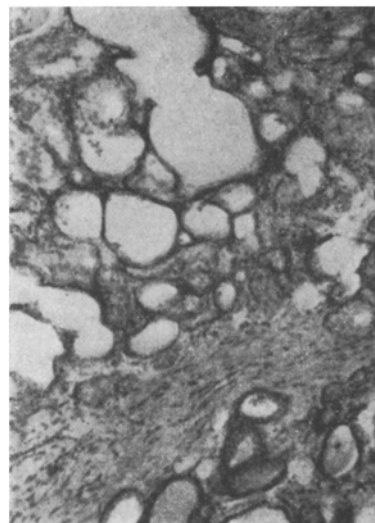


Fig. 2

Fig. 2. Absence of marked round-cell infiltration of thyroid homograft in rabbit 10 days after operation. Experimental group. Hematoxylin-eosin, 80 $\times$ .

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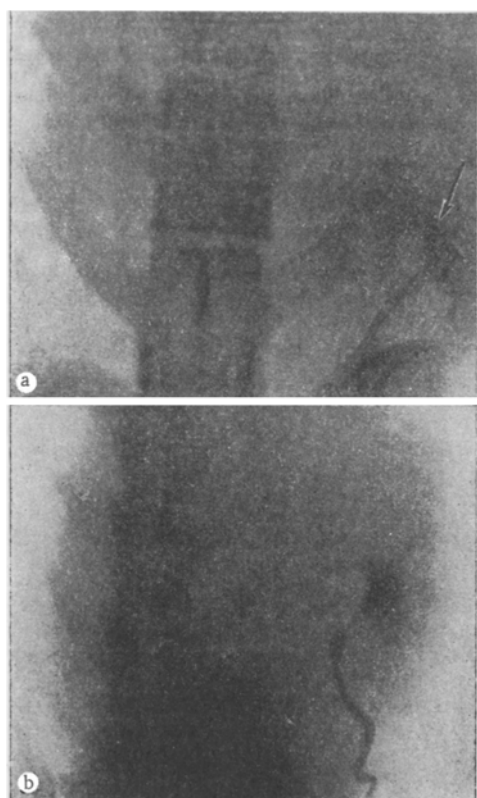


Fig. 3. Excretory (a) and retrograde (b) pyelogram of a kidney homograft 10 days after transplantation. Experimental group. Arrow indicates pelvic shadow.

of the thyroid in rabbits was the same as that described previously [1, 2]. Operations were performed on 16 rabbits subdivided into the following groups on the basis of the time of investigation: 10 days, 6 animals; 15 and 25 days, 4 animals each; and 72 days, 2 animals. Eight rabbits constituted the control group and 8 the experimental group. These animals received 2.5 mg thio-TEPA/kg body weight daily for 10 days after the operation. At the times specified above the rabbits were sacrificed and the grafts studied morphologically. In the second stage of the investigation, kidneys were grafted into dogs. Altogether 12 operations were performed, 4 dogs were under observation for 10 days, 6 for between 12 and 14 days, and 2 for 16 days. The experimental animals received thio-TEPA in a daily dose of 0.3 mg/kg body weight and hydrocortisone in a daily dose of 5 mg/kg body weight for 10 days. Kidneys were grafted onto the iliac vessels and the ureter brought out onto the thigh. The left kidney was removed from the recipients. The grafts were studied histologically and their function was tested.

### EXPERIMENTAL RESULTS

The grafted thyroid glands in the rabbits of the experimental group 10 days after transplantation showed severe structural changes. The follicular architectonics of the gland tissue remained intact. However, many follicles contained no colloid, while in others it was not stained. The epithelial cells of the follicles were considerably flattened, and their nuclei could not be clearly distinguished against the background of the cytoplasm because of its poor staining properties. The distinguishing feature of the microscopic structure of homografts in animals of the experimental group compared with the controls was the slight degree of lymphocytic infiltration (Figs. 1 and 2).

At later periods (on the 16th and 25th days after transplantation) the well-formed glandular tissue in homografts in the experimental animals occupied an area equal to half the initial extent of the transplanted gland. This regenerating fragment of thyroid tissue was situated very close to the main source of its nutrition: the iris. In the control homografts the glandular tissue usually disappeared by the 16th day. Where the gland had been, cyst-like structures were found, devoid of epithelium and surrounded by proliferating connective tissue.

The results of the kidney transplantation experiments were as follows: 4 control dogs died 8-10 days after the operation, 4 experimental dogs survived 14-16 days after transplantation, and 2 dogs of this group were sacrificed earlier for histological control investigations.

Comparison of the histological structure of the kidney homografts in the control and experimental groups up to 10 days after transplantation showed significant differences, primarily in relation to the intensity of round-cell infiltration. This was a constant structural element of the kidney homografts in the control animals. Zones of infiltration were found most frequently in the parenchyma surrounding the renal glomeruli, in the lumen of the glomeruli, and between the inner and outer membranes of Shumlyanskii's capsule. In the renal medulla, lymphocytic infiltration was much less marked. Focal hemorrhages, located mainly in the subcapsular and cortical layers of the kidney, were a constant feature on microscopic examination of all the grafts. They were much less frequent in the medullary layer of the renal parenchyma. No significant changes were found in the early periods in the structure of the tubular epithelium.

At later periods (10-14 days after transplantation) degenerative changes such as karyolysis and cytolysis, together with round-cell infiltration, were found much sooner and they were more marked than in homografts from the experimental animals.

The results of the histological investigations were reflected in disturbances of function observed in these experiments. By the 7th day after operation, only 5 of the 12 grafts were functioning (4 in the experimental animals and 1 in the controls), although during the first 3 days no quantitative difference was observed between them. Posttransplantation anuria occurred in experiments in which renal ischemia persisted for longer than 70 min.

The concentrating power of the grafted kidney, once it had started to function, was studied in two animals and was disturbed, the excreted urine having a low specific gravity and containing large quantities of protein and leukocytes. The indigocarmine test, carried out on one dog, was positive although the intensity of coloring of the urine was too low. Methiodal sodium elimination tests carried out on two grafts in experimental animals 10 days after the operation were satisfactory (Fig. 3).

The experimental results thus indicate that no significant qualitative differences are found in the evolution of kidney and thyroid grafts transplanted by different methods (on a vascular pedicle or not) after the 10th day. The length of survival of thyroid homografts was increased by the action of thio-TEPA from 16 to 25 days, and this can be correlated with the less marked cellular response of the recipient.

Combined administration of thio-TEPA and hydrocortisone postponed rejection of kidney homografts until 14-16 days (compared with 8-10 days in the control). This prolongation effect must be attributed mainly to the action of thio-TEPA which, by inhibiting lymphoid infiltration, prevents earlier rejection of the homografts. Hydrocortisone, with its antiproliferative action, during these relatively short times cannot be the principal factor in prolonging survival, because fibrosis of the grafts, as a manifestation of incompatibility, usually develops later.

#### LITERATURE CITED

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