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RELATIONSHIP BETWEEN CORTISONE DOSE AND ACQUIRED TOLERANCE IN HOMOTRANSPLANTATION

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In a previous paper [11] it was reported that on treatment with 15 mg of cortisone, administered in 2,5 mg doses on 6 occasions every other day, 80 per cent of our homotransplants of adult thyroid glands to both normal and thyroidectomised host rats had proved successful. So far a 436-day transplant has been the oldest successful one. This transitional cortisone treatment, which protects the transplant from the reactions of the host, has been termed by us treatment with the adaptive dose of cortisone. On the evidence of our further investigations [12] we have supposed, that the above-mentioned "adaptive dose" exercises its effect by a form of acquired tolerance.

The purpose of the present work was to establish if a dose of less than 15 mg would equally suffice to protect the transplant.

Methods

A homoio-thyroid lobe was transplanted into a pouch prepared under the skin of the back of thyroidectomised, not pure-bred white rats of both sexes, weighing 140 to 160 g. The skin incision was closed by stitches. Following transplantation the animals were divided into three groups and each was given 2.5 mg of cortisone (Adreson, Organon) on 4 alternate days in the first group, on 2 in the second, and on a single occasion in the third, totalling 10 mg for the first, 5 mg for the second, and 2.5 mg for the third group. When the transplants were 60 days old, they were worked up in serial sections, and so were the residual thyroid glands of the hosts. By the end of that time, the central necrosis and the accompanying organisational reaction, which because of the temporary nutritional disturbances are present in every transplant, were certain to have passed off. Experience shows that 20 to 30 days suffice for this to take place.

Results

On the histological evidence, every one of the transplants in the three experimental groups could be classed with either of the following three types.

Type I. This was the successful transplant which satisfied all the conditions fixed in our previous paper [11]. It was perfectly free from inflammation and lympho-plasmo-cellular or eosinophilic infiltration. The transplanted gland corresponded in every respect to the intact gland and functioned just like the host's own residual thyroid (Fig. 1). The parathyroid attaching to the thyroid gland likewise retained its structure.

Type II. The parenchyma of this type of transplant presented the same picture as that of Type I, but the entire gland was so densely interwoven with lymphocytic infiltration as almost to obscure at places the histological picture (Fig. 2). Occasional fibrotic foci were observed.

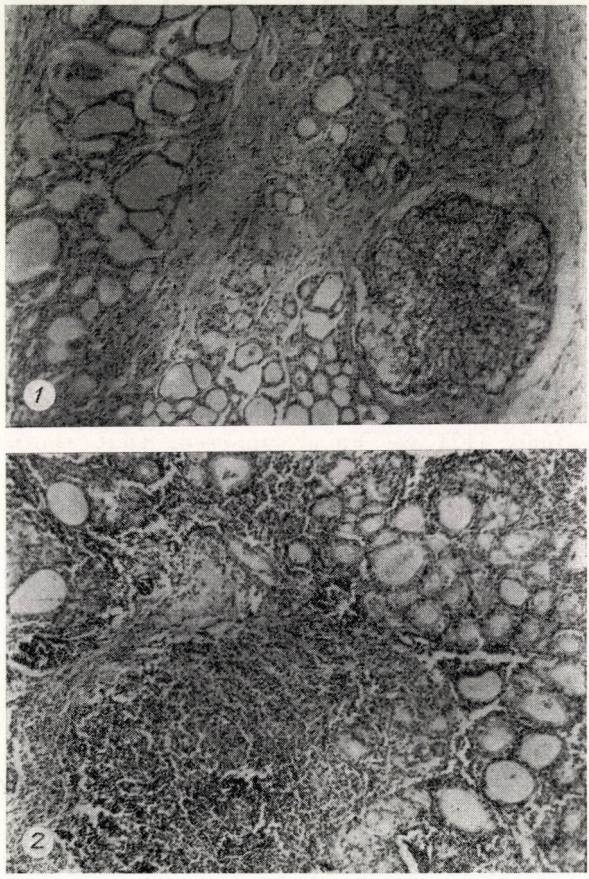

Fig. 1. First group. Type—I. transplant, entirely free from inflammation, with central cicatrization and intact parathyroid. (Bottom right corner.) HE., × 80

Fig. 2. Second group. Type—II. transplant densely interwoven by lymphocytes and eosinophils. The relatively intact follicles are seen to be pushed apart by the infiltration. HE., ×80

Type III. In transplants of this type it was not possible to recognize the tissues of the thyroid and parathyroid. They were thoroughly fibrotic, with sporadic lymphocytic foci and groups of siderophagous cells.

The following Table shows the distribution of each of these types of transplants over our three experimental groups.

Exp. group. No	Cortisone dose in mg	Number of animals in group	Type		
			I	II	III
1	10	13	1	6	6
2	5	12	1	9	2
3	2,5	11	0	8	3

This Table shows that from a total of 36 animals, only one in each the first and second group yielded a succesful transplants of Type I.

Discussion

Numerous authors administered cortisone to have the transplants protected, but it is clear from their communications that, apart from a few special cases, only continuous cortisone treatment ensured viability, while cessation of the treatment involved the death of the transplants [1, 8, 10, 13, 22, 27]. Only when tumour material was transplanted [16, 19, 23, 24], or newborn animals were used [6], did temporary treatment, similar to the one applied by us, produce successful takes. Although implanted tumour material elicits from the host the same immune-biological defense as implanted normal tissue, the two transplantations cannot be identified unconditionally. Two moments of mutually opposing action must be taken into account, viz. defense by the host and vitality or growth rate of the transplant. With the later intense, a minor inhibition of the former will suffice to make the transplant take. Such conditions exist only when certain types of tumour are transplanted ; TOOLAN [25] encountered takes upon a single dose of cortisone exclusively with tumours of exceedingly rapid growth. According to her, if protected for a short time from immune reactions, a tumour of intense growth will be able to resist by its very mass the immune reactions which later again begin to act.

As regards transplantations in newborns, a very moderate inhibition of the immune response was of course sufficient, since the animals were still at a stage of life when they can give no or only slight immune reactions [4, 5, 7, 8, 9, 10, 14, 15, 17, 18, 20, 21, 26].

The results we had obtained with the adaptive dose of cortisone gave rise to the theoretical question wether similar results were obtainable with lesser doses, and to the practical question whether clinically it were possible to apply lesser quantities of cortisone. On the evidence of our findings, amounts less than 15 mg per 100 g failed to yield appreciable proportions of successful transplants, and this fact precluded any reduction of the adaptive dose. In

our previous paper [12] the explanation for the role of this dose in the inhibition of the host's defensive reactions was that it gave rise to a form of acquired tolerance. Since, just while massive cortisone treatment is profoundly destroying the protective system of the host, the transplant is recovering from the non-immune-biological injuries associated with transplantation and due to nutritional disturbances, and is becoming integrated into the organism of the host. The protective system destroyed is forced to regenerate from the reserve cells, as though to go once more through the embryonic developmental process. In this manner, the transplanted thyroid is present in the organism of the host at the time the protective apparatus is forming again, and thereby acquired tolerance can set in. The conditions for this are essentially the same as those in the experiments of BILLINGHAM et al. [2].

In applying this hypothesis to the present work, our assumption is that in the tissues giving immune response smaller doses fail to cause as profound a destruction as the 15 mg dose of cortisone capable of permitting the appropriate degree of tolerance to develop.

In discussing our findings there are two points that merit theoretical interest. One is that the results obtained were about identical in all three experimental groups. This fact indicates that below a certain limit (a total of 15 mg) results are essentially independent of differences in the amount of cortisone administered. The other point is that the unsuccessful transplants belonged in their majority to Type II. In contrast to Type III, they can be conceived of as transplants which had been temporary successes until the defensive reactions of the host got mastery over them, or in which at the time of the histological examination, i. e. on the 60th day after transplantation, the struggle between the host's immune reaction and the transplant was still in progress. While in our earlier examinations [11] it was found that without cortisone treatment all the transplants were thoroughly destroyed by the 30th day, in our present experiments only about one third of them showed a picture of utter destruction even as late as on the 60th day. Obviously, little in the tolerance induced by BILLINGHAM et al. [2, 3] in the embryonic stage, in the acquired tolerance arising upon the action of the adaptive dose of cortisone, it is not the "all or nothing" principle that asserts itself, since a smaller dose of cortisone was found to give rise to an easily disappearing limited tolerance.

Summary

Adaptive treatment of thyroidectomised rats with various doses of cortisone less than 15 mg failed to elicit a sufficiently high degree of lasting tolerance for homotransplants of thyroid glands. Reductions in dosage were followed by decreases in tolerance, the latter merely retarding destruction of the transplant.

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СВЯЗЬ МЕЖДУ ВЕЛИЧИНОЙ ДОЗЫ КОРТИЗОНА И СТЕПЕНЬЮ ПРИОБРЕТЕННОЙ ВЫНОСЛИВОСТИ ПРИ ГОМОТРАНСПЛАНТАЦИЯХ

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Введением различных доз кортизона ниже 15 мг в целях адаптации авторам не удалось вызвать у животных с удаленной щитовидной железой соответствующей и длительной выносливости в отношении к гомотрансплантатам щитовидной железы крыс. Уменьшенная доза обусловливает выносливость меньшей степени, которая сказывается лишь в запоздалой гибели трансплантата. Авторы объясняют данное явление меньшим разрушением тканей, ответственных за имунную реакцию.

ZUSAMMENHANG DER CORTISONDOSIS MIT DER ERWORBENEN TOLERANZ BEI HOMÖOTRANSPLANTATIONEN

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An thyreoidektomisierten Tieren konnte durch Adaptationsbehandlung mit verschiedenen — kleineren als 15 mg — Cortisondosen keine entsprechende, anhaltende Toleranz gegenüber Homöotransplantaten von Rattenschilddrüsen erzielt werden. Auf Wirkung von kleineren Dosen entsteht eine geringere Toleranz, die das Zugrundegehen der Transplantate bloss verzögert. Die Erscheinung wird mit dem verminderten Absterben der für die Immunreaktion verantwortlichen Gewebe erklärt.

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