Transfer of Acquired Tolerance to Skin Homografts in Mice.* (24134)

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The induction of acquired tolerance to homotransplantation of several kinds of tissues in animals of different species treated at birth with living foreign spleen cells has been firmly established(1,2,3,4,5). However not much is known as to the mechanisms involved in the induction or maintenance of this immunological phenomenon. Based on our observations on tolerance in mice to homologous tumors inoculated during their neonatal period, it was tentatively postulated that persistence of immunological tolerance might be dependent on presence of foreign living cells in the tolerant individual(6). These observations suggested that one way to test this hypothesis would be to transfer tolerance by way of spleen cells taken from a tolerant animal, by injecting these cells into newborn individuals of the same strain. Specifically, the purpose of these experiments was to ascertain whether or not acquired tolerance induced in "B" strain individuals to "A" strain tissues could be transferred to other animals of the "B" strain by intravenous injection at birth of spleen cells taken from "B" adult donors previously made tolerant to "A" strain tissues.

Method. Inbred mice of the ZBC‖ and Ce stocks were used. ZBC animals are backcross hybrids to the Z(C3H) strain and genetically non-related to those of the Ce strain. In a first step, tolerance to Ce skin homograft was induced in ZBC animals by intravenous injection at birth (not later than 24 hours) of 2-4 million living spleen cells taken from adult Ce donors. The method of preparation of the spleen cell suspension and that of intravenous injection has been described previously(5,7,8). When treated animals were approximately 2 months of age or older, they received a full thickness skin graft taken from adult Ce donors. Technic for skin graft and criteria used to judge its success or failure have also been described(5). Treated ZBC animals accepting the skin graft for no less than 2 months were considered as tolerant to Ce tissue and used as donors of the spleen to be used in second part of experiment. This consisted essentially in removal of spleen from ZBC animals which were tolerant to Ce. These spleen cells were then prepared as a new spleen cell suspension which was injected into newborn animals of the ZBC strain. The preparation of these cells and the injection were performed as in the first phase of the experiment. When this second group of animals were approximately 2 months old they were tested for tolerance to skin grafts taken from adult Ce donors. A group of non-treated ZBC animals also received a Ce homologous skin graft and served as controls.

Results are listed in the Table. The incidence of successful Ce skin grafts in ZBC animals injected at birth with living spleen cells taken from Ce donors was 94% of a total of 35 mice tested. Similarly the incidence of successful Ce skin grafts in ZBC animals injected at birth with living spleen cells taken from ZBC donors made previously tolerant to Ce tissues was 83% from a total of 30 animals. The difference between this incidence and that in the former group is not statis-

TABLE I. Transfer of Tolerance to Skin Homografts in Mice.

Spleen donor strain	Recipient strain	Skin grafted	No. of mice accepting skin graft
			%
Ce	ZBC	Ce	33/35 (94)
ZBC tol. Ce	"	"	25/30 (83)
	"	"	0/66 (0)

* Aided by grants from Minnesota Division of Am. Cancer Soc., and the U.S.P.H.S.

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‖ ZBC hybrids are obtained as follows:
A ♀ x Z(C3H) ♂ = AZ F_1 ♀ x Z(C3H) ♂ = ZBC

tically significant. In contradistinction the 66 non-treated ZBC controls all rejected the Ce homologous skin as would be predicted from their genetic differences.

Discussion. Our results agree with the hypothesis which provoked this study. In fact, it was originally postulated that if the state of tolerance requires the presence of living foreign cells in the host it might be possible to transfer this tolerance to another individual of the same strain by injecting at birth the spleen containing the homologous foreign cells necessary to induce this phenomenon. Our observations using the donor-host strain combination Ce⟶ZBC indicate that this has been accomplished, since by treating newborn ZBC animals with living spleen cells taken from ZBC animals tolerant to Ce donor, tolerance to homologous Ce skin was demonstrated.

This observation also agrees with that of Billingham, Brent and Medawar(2) who showed that spleen tissue from tolerant animals contains antigenically active material from the donor strain. Our findings however extend those of the British workers and indicate that in the tolerant host all of the transplantation antigens presumably in the form of many intact cells derived from the original donor are present in the reticuloendothelial tissues of the tolerant host.

Summary. Newborn mice of the ZBC strain injected intravenously with living spleen cells taken from donors of the same strain in which tolerance to Ce tissues was previously induced, became tolerant to this strain and accepted homologous skin grafts from Ce donors. This would indicate that acquired tolerance can be transferred to an isologous individual at birth by the intravenous injection of spleen cells taken from a tolerant donor.

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Received May 21, 1958. P.S.E.B.M., 1958, v98.

Hypothalamus and Somatotrophic Hormone Release. (24135)

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Hypothalamic control of somatotrophic hormone (STH) secretion, though not yet clearly demonstrated, may be assumed from data in the literature. Hetherington *et al.*(1), Bogdanove *et al.*(2), and Endröczi *et al.*(3) showed that rats with hypothalamic lesions frequently fail to grow; retardation of body growth has also been reported in dogs in which anterior hypothalamic lesions had been performed early in their life(3). Typical disturbances of carbohydrate metabolism induced by hypophysectomy and by STH deficiency have been found also after hypothalamic lesions involving the region of paraventricular nuclei(4); Spirtos *et al.*(5) observed that lesion-bearing rats often exhibit increased hypoglycemic response to insulin, which can be reduced by STH administration. It is generally agreed that marked retardation of body growth follows transplantation of the pituitary far from the sella turcica (6,7); it is noteworthy that both hypothalamic lesions(2) and hypophyseal transplantation(7) induce disappearance of the STH-producing eosinophil cells of the anterior pituitary. The mechanism by which hypothalamic stimuli may reach the glandular cells of the anterior lobe of the pituitary gland