A Thymus Dependent Function of the Adrenal Cortex and its Relation to Immunity

Neonatal thymectomy in mice and in some other species results in severe impairment of immunological capacity and in particular of cell-mediated immunity. Also congenitally thymusless 'nude' mice show a remarkable deficiency both in their capacity to respond to certain antigens and to reject histoincompatible tissues[1-4]. Therefore, both types of experimental animals present characteristics useful for studying the function of the thymus in the development of the immune capacity in ontogeny.

Hormones from several endocrine glands have been shown to exert a profound effect on the thymo-lymphatic tissue and on the immune response. We have suggested previously that an interrelation exists between the development of the immunolymphatic and the endocrine system in ontogeny[5-8]. In order to clarify the nature of the link between some endocrine glands and the thymus, we have examined the possible role of the thyroid, the adrenal cortex and of the hypophysis in athymic nude mice.

We would like to propose here that 1: the thymus acts as an endocrine organ in ontogeny, promoting the differentiation of other endocrine glands and that 2: the immunological function of a mature animal is directly dependent on the function of the thymus as an endocrine gland in early ontogeny to promote maturation of other endocrine glands in early life.

The adrenal foetal zone and the thymus. We have recently found that athymic nude mice show an alteration of the structure of the adrenal cortex. Young (3- to 4-week-old) and adult (5- to 10-week-old) athymic mice show a marked enlargement of the reticular zone. This zone disappears in coincidence with the precocious 'wasting' and death of these mice[9]. In normal mice, no reticular zone in the adrenal cortex is present at birth. This zone develops later, especially concurrent with the striking increase in adrenal weight which starts at the beginning of the second week and continues through the third week of age, at which time there is a virtual cessation of body growth[10]. The factors regulating the growth of this zone of the adrenal cortex are not known and its function is obscure.

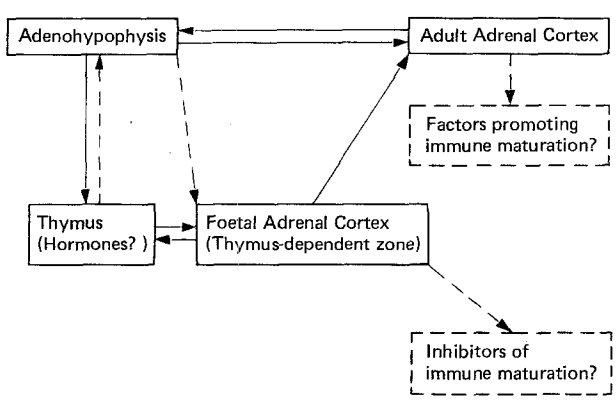
In humans, the foetal adrenal gland, the weight of which is proportionately 10 to 20 times higher than that of the adult gland, is largely composed of a clear reticular zone which involutes by necrosis after birth[11]. The reticular zone of the adrenal cortex of the human foetus, known as the 'foetal zone', can well be compared to the reticular zone appearing and increasing in the adrenal cortex of the mouse after birth. Also the function of this zone in the adrenal cortex of the human foetus is unknown[12].

In rat foetuses a reticular zone is visible in the adrenal cortex already at 16 days of gestation[13,14]. This zone enlarges steadily, together with the other zones of the cortex. At birth, as in humans, there is a very marked decrease in cortical volume mainly due to shrinkage of the cells of the zona fasciculata and reticularis. However, while the cells of the fasciculata only shrink, the cells of the reticularis gradually disappear. This is similar to the human foetus at birth. Therefore the reticularis of the adrenal cortex of the rat foetus can be compared to the foetal zone of the adrenal cortex of the human embryo.

The nature and significance of these morphological changes in the function of the adrenal gland are obscure as is also the function of the reticular zone of the adrenal cortex in mammals. Contrary to the zona fasciculata and similarly to the zona glomerulosa, the zona reticularis does not seem to be dependent on hypophysial hormones for its growth and function. Rather it seems to depend on some other unknown factors which also affect the function and structure of the adrenal cortex in ontogeny, including that of the foetal zone of the human adrenal gland. It is our proposal that such factors are at least to some extent derived from the thymus (see following section and our previous paper[9].)

Normalization of adrenal glands of nude mice by transplantation of normal adrenals. In order to investigate whether the structural abnormality of the adrenal cortex of the athymic nude mice might be corrected by implantation of the thymus or of normal adrenal glands, thymus and/or adrenal glands from normal haired young mice (4- to 8-week-old) were transplanted into the axillary cavities of young adult nude recipients (4- to 6-week-old). 2 or 3 weeks after the implantation, the animals were killed and the implanted thymuses or adrenal glands and the adrenals of the recipients examined histologically.

Implantation of both the normal thymus and normal adrenal glands into the nude mouse results in normalization of the structure of the adrenal cortex of the recipient nudes. Implantation of the thymus only does not result in a regression of the width of the enlarged reticular zone, while nude mice transplanted with 2 adrenal glands from normal donors show a normal structure of their adrenal cortex. Therefore, the adrenal glands



Proposed relationship between thymus and adrenal cortex in ontogeny.

[1] E. M. Pantelouris, Nature, Lond. *217*, 370 (1968).
[2] J. Rygaard, Acta path. microbiol. scand. *77*, 761 (1969).
[3] J. Rygaard and C. O. Povlsen, Acta path. microbiol. scand. *77*, 758 (1969).
[4] H. H. Wortis, Clin. exp. Immun. *8*, 305 (1971).
[5] W. Pierpaoli and E. Sorkin, Nature, Lond. *215*, 834 (1967).
[6] W. Pierpaoli and E. Sorkin, *Antibiotica et Chemotherapia* (Ed. E. Sorkin, Karger, Basel 1969), vol. 15, p. 122.
[7] W. Pierpaoli, N. Fabris and E. Sorkin, in *Hormones and the Immune Response*. Ciba Foundation Study Group No. 36 (Ed. G. E. W. Wolstenholme and Julie Knight, Churchill, London 1970), p. 126.
[8] W. Pierpaoli, Elena Bianchi and E. Sorkin, Clin. exp. Immun. *9*, 889 (1971).
[9] W. Pierpaoli and E. Sorkin, Nature Lond., in press.
[10] Florence Moog, C. J. Bennett and C. M. Dean jr. Anat. Rec. *120*, 873 (1954).
[11] J. T. Lanman, Endocrinology *61*, 684 (1957).
[12] J. T. Lanman, Medicine *32*, 389 (1953).
[13] J. B. Josimovich, A. J. Ladman and Helen Wendler Deane, Endocrinology *54*, 627 (1954).
[14] Arnolda W. V. van Dorp and Helen Wendler Deane, Anat. Rec. *107*, 265 (1950).

of normal mice seem to produce some factor(s) which compensate for the deficiency of the adrenal cortex of the nude mice. The reticular zone of their glands, which is enlarged probably in the sense of a compensatory hypertrophy or hyperplasia, regresses to a normal width. As reported in a previous paper[9], implantation of the neonatal thymus into newborn nude mice prevents such alterations of the adrenal cortex. Thus the neonatal thymus in mice seems to control the differentiation of a 'thymus-dependent zone of the adrenal cortex', but once the alteration of the cortex is established, implantation of the adult thymus into adult animals cannot induce a reversal of the alteration. In this case, only the same factors which are present in the normal adrenals seem to be able to reverse the enlargement of the reticular zone of the immature adrenals of the nude mouse. As discussed above, the adrenal cortex of the mouse in the postnatal time can be compared to that of the human foetus where the reticular zone is extremely developed and disappears suddenly at birth. In our case, it appears that the thymus in the mouse produces factors in ontogeny which promote maturation of the adrenal glands in coincidence with maturation of the immune capacity. It is therefore probable that some adrenal factors, produced in that section of the adult adrenal cortex which was thymus-dependent for its maturation, are promoting the immunological maturation of incompetent thymus-derived or bone marrow-derived lymphocytes.

Endocrinological and immunological implications. The thymus is considered as the organ where formation of the lymphocytes which are responsible for cell-mediated immunity occurs. This type of immune response is particularly deficient in the congenitally athymic mice. As cell-mediated immunity in mice at birth is much less developed than in humans and the absence of the thymus in athymic nude mice seems to be responsible for the extreme enlargement of the reticular zone of the adrenal cortex, a correlation between the thymus, the foetal or immature adrenal cortex and the development of the immune capacity in ontogeny is likely to exist. In agreement with this, we have found that the adrenal alterations in the athymic mice can be prevented by neonatal implantation of the thymus[9]. This suggests that the thymus in ontogeny is regulating the development of some zones of the adrenal gland. These zones might produce factors, some of which first may prevent and later on promote, the differentiation of lymphocytes to immunocompetent cells. These factors are probably produced by the reticular or foetal zone of the immature adrenal glands and by the mature adrenal glands of adult animals (Figure).

The function of the thymus in ontogeny might be that of promoting the differentiation of the adrenal gland from the foetal to the adult structure and function. This change of the thymus-dependent adrenal function in neonatal and postnatal life does probably depend on a change of factors released by the adrenal glands. The fact that young nude mice are unable to reject skin grafts in spite that the number of their peripheral lymphocytes can still be up to 50–60%, seems to indicate that, not the number, but the function and the capacity of the lymphocytes is important for the animal to mount a cell-mediated immune reaction. The absence of the thymus in the nude mice prevents the maturational changes in the adrenal cortex to occur and their cell-mediated immune responsiveness remains as deficient as in newborn mice. Therefore, absence of the thymus may prolong the foetal state of immaturity of cellular immunity because the differentiative action of the neonatal thymus on the adrenal gland cannot be exerted and the adrenal cortex cannot produce the factor(s) which are necessary to promote the transformation of the lymphocyte from an unreactive to a fully immunoreactive cell. The above data to suggest that, not only the absence of the thymus in nude mice, but possibly the lack of differentiation of the thymus-dependent zone of the adrenal cortex is responsible for their deficiency in cellular immunity.

Another argument is that the reticular zone of the adrenal cortex which is so developed in the human foetus and in the nude mouse is possibly secreting a factor which inhibits immune functions of lymphocytes and prevents, e.g. during foetal development in humans, an immune reaction of the foetus against the mother which would seem possible on the basis of the development of the thymo-lymphatic tissue in the human embryo. At birth, the dramatic disappearance of the foetal zone or reticular zone would eliminate this inhibiting factor being produced and the human newborn would become fully immunocompetent. From this point of view, the rat foetus seems to be more similar to the human than to the mouse foetus[13,14]. Some experimental work supports this suggestion[15].

The hormones of the adult adrenal gland that promote differentiation of the immune lymphocytes are probably some of the known hormones of the adrenal cortex. On the contrary, the identification of the factors which might be present in the foetal zone of the adrenal cortex in humans is necessary. Also more study of the factors in the thymus promoting the differentiation of the adrenal gland from the foetal to the adult structure and function is indicated. Thus the possibility exists to identify presumably hormonal factors which are both crucial for stimulating or preventing immune responsiveness.

Zusammenfassung. Es wird vorgeschlagen, dass der neonatale Thymus in Mäusen die Differenzierung einer foetalen Thymus-abhängigen Zone der Nebennierenrinde zur erwachsenen Struktur und Funktion kontrolliert. Die mögliche Bedeutung dieser Befunde für die hormonelle Kontrolle des Immunsystems in der Ontogenese wird diskutiert.

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[15] H. O. BESEDOVSKY, Experientia 27, 697 (1971).

Free Flow Electrophoresis of Isolated Secretory Granules from Bovine Neurohypophyses

Recently some evidence has been presented that the secretion of the hormones vasopressin and oxytocin from the mammalian neural lobe of the hypophysis occurs by exocytosis, that is a fusion of the membrane surrounding the neurosecterory granules with the plasma membrane of the nerve terminals, followed by a perforation of the membranes, allowing the contents of the neurosecretory granule to leave the cell (for a review see DOUGLAS et al.[1]).