CERTAIN DATA ON THE DEVELOPMENT OF THE ADRENAL AND THYMUS GLANDS IN HUMAN EMBRYOGENESIS

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It has been shown that alkaline phosphatases appear in the intestinal epithelium when corticoids begin to be secreted from the adrenals, that they disappear during adrenalectomy and are not dependent on the character of their nourishment and that their content is linked with the level of corticoids in the blood [8, 13].

In the present investigation experiments were made to demonstrate correlations between the adrenals and the thymus gland during intrauterine development of the human fetus.

METHODS

The activity of alkaline phosphatase in the intestinal epithelium of the fetus is determined by the Gomori reaction which shows the corticoid level in the fetal blood.

One hundred and fifty-five fetuses, 9-40 weeks old, were kept in the cold for two to eight hours before being examined. The wall of the duodenum was fixed in neutral formalin at +5° for 10-12 h and then frozen sections were tested by the Gomori reaction (incubation in sodium β-glycerophosphate for two and a half hours). The thymus and adrenal glands were weighed and prepared according to the usual histological methods.

RESULTS

Alkaline phosphatases are not found in the duodenal epithelium of the 9-11 weeks old fetus of either sex. At the 12-13th week, enzymes begin to accumulate in the cells of individual villi and, as the embryo grows, so the number of such villi increases, but even in the 16-17th week the accumulation of phosphatases exhibits a focal character and the intensity of the reaction is weak. Towards the 18-20th weeks, villi containing active enzymes are predominant. Beginning with the 21st week up to the time of birth, the Gomori reaction shows that the whole of the mucous membrane of the duodenum is filled with a black deposit of cobalt sulfide. The reaction grows not only in extent but in intensity. It is interesting to note that there seems to be a reduced enzyme activity in the crypts and phosphatases are completely absent from the Brunner's glands and goblet cells (Fig. 1). From the 25th week, break-away epithelial cells, having a very high phosphatase activity in the cytoplasm are sometimes observed in the aperture of the duodenum. The boundary between the mucous membrane of the stomach with its complete lack of phosphatases and the duodenal epithelium with its high phosphatase activity is very distinct; the pyloric sphincter area appears to be a definite limit to the spread of the enzyme (Fig. 2).

In order to check the role of the maternal hormones in this reaction, adrenalectomy was performed on guinea pigs on the 53rd-54th day of pregnancy. The activity of alkaline phosphatase was very high in the duodenal epithelium of the fetus for two days (the mother died at the end of two days).

Thus, if the accumulation of alkaline phosphatases in the duodenal epithelium reflects the activity of corticoid secretion from the adrenals, as was shown in Moog's [8] experiments, it could be considered that during embryogenesis in man the flow of corticoids into the blood begins in the 12-13th week, grows slowly up to the 20th week, and, thence, from the 21st week, sharply increases and remains at a high level until the birth of the infant. This

Fig. 1. Duodenum of the human fetus, 22 weeks old. There is a high activity of alkaline phosphatases in the epithelium of the villi and a somewhat lower one in the crypts. The reaction in the Brunner's glands and goblet cells is negative. Microphotograph. Gomori reaction for alkaline phosphatases. Ocular x 10, Objective x 20.

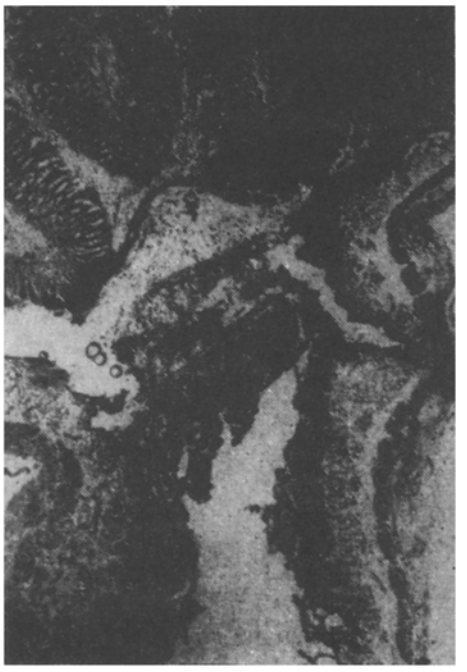

Fig. 2. Pyloric section of the stomach (sphincter area) and beginning of the duodenum of the human fetus, 30 weeks old. There is a high activity of alkaline phosphatases in the duodenal epithelium but the epithelial glands in the stomach are void of any trace of enzyme. Microphotograph. Gomori reaction. Ocular x 10, Objective x 8.

last period coincides with a definite morphological shift in the adrenals; in the 20th week the fetal cortex loses lipoids and from the 21st-22nd week they accumulate in the fully developed cortex [1, 2].

No success was obtained in establishing any kind of relationship between these data and the changes in the weights of the adrenal and thymus glands and also their morphology. At the beginning of the second quarter of intrauterine life the thymus gland in the fetus is an accumulation of epithelial and reticular cells with connective-tissue trabeculae dividing up the tissue. In the 12-13th week, a few cells similar to thymocytes can be distinguished. In the 13-15th weeks narrow, cortical layers, rich in thymocytes, are formed around the central parts which are filled with epithelial tissue. However, these relationships do not remain unchanged throughout embryogenesis; in the 15-18th weeks the number of thymocytes in the cortex appears to decrease and from the 20th-21st week it increases but later, in isolated individuals, the cortex proves to be poor in thymocytes.

Already, in the 15-17th weeks, Hassal's corpuscles appear in the epithelial centers as round, concentric, corneous, acidophilic masses of various sizes. Later, on throughout the whole of embryogenesis, they are met with in the majority of fetuses but no relationship between their number and the growth and sex of the fetuses has been established.

The large cells met with in the connective-tissue trabeculae and which separate the lobules of the thymus gland are interesting; their cytoplasm is crammed with a coarse granulation which stains well with azocarmine. These cells are sometimes met with singly, sometimes in groups, seldom within the trabeculae but in the tissue of the lobules, in close proximity to the trabeculae. Similar cells have not been observed in other embryonic tissues. In the thymus gland they appear during the 15-16th week of development and later on, in many (but not in all) fetuses, they are found throughout embryogenesis. No relationship could be found between the age of the fetus and its sex or the condition of the thymus gland.

Absolute and Relative Weights of the Adrenal and Thymus Glands in the Female Human Fetus

Age (in weeks)	Average weight (g)	Adrenals		Thymus gland		Number of fetuses examined
		Absolute weight (mg)	Relative weight (%)	Absolute weight (mg)	Relative weight (%)	
13	55.75	255	4.57	62.75	1.13	2
14	69.90	372	5.33	62.0	0.88	2
16	89.0	335	3.76	66.0	0.74	2
17	105.0	652	6.20	98.0	0.93	4
18	161.0	748	4.65	252.0	1.57	4
19	191.0	1,070	5.60	258.0	1.35	3
20	261.0	1,627	6.23	507.0	1.94	6
21	356.0	1,830	5.15	611.0	1.73	9
22	440.0	1,809	4.13	736.0	1.67	9
23	549.0	2,286	4.17	1,293.0	2.36	12
24	654.0	2,899	4.44	1,697.0	2.60	5
25	710.0	2,866	4.04	2,022.0	2.84	6
26	848.0	3,983	4.70	2,093.0	2.47	3
27	979.0	2,960	3.02	4,100.0	4.20	2
28	1,190.0	3,220	2.71	2,940.0	2.47	2
31	1,380.0	3,580	2.59	3,400.0	2.46	1
32	1,760.0	5,170	2.94	5,840.0	3.31	2
36	2,400.0	4,600	1.92	4,970.0	2.08	1
40	2,496.0	9,806	2.82	13,600.0	3.89	5

The variations in the weights of the thymus and adrenal glands in the course of intrauterine development of the female fetus are given in the table. It can be seen that there is also no relationship between the weights of the glands during this period. No correlation was observed between the weights of the thymus and adrenal glands in an examination of the glands in the fetal guinea pig.

The morphogenesis of the anencephalous fetus is of extreme interest in a study of the endocrine correlations during human embryogenesis. The hypophysis in this fetus is imperfectly developed; according to Covell's data [5], the nervous portion is absent in two thirds of the fetuses examined, while according to Angevine [3] the proportion is 80%. The anterior portion is usually present but is often reduced in size. The constant absence of the hypothalamic region precludes the normal functioning of the adenopophysis in the anencephalus. Authors who have studied this monstrosity have put forward a consistent picture of the pathology of the endocrine system: atrophy of the adrenals (one seventh of the weight of the normal fetal glands) accompanied by a reduction of the fetal cortex. At the same time, the normal histo-structure of the thyroid, thymus, adrenal and sex glands not only show no signs of atrophy but the glands are heavier (sometimes more than twice) than those in the normal fetus [3, 4, 6, 12]. Thus, according to the data of certain authors [12], the average weight of the thymus gland in 66 normal fetuses in the second half of development amounted to 4.78 g, but in the anencephalous fetus during the same period the weight was 10.37 g. The corresponding weights of the adrenals were 3.51 and 0.55 g. In comparing the data given in the table with unaveraged figures cited by each individual [6], it is seen that in the 17th week of development the adrenals in the anencephalus are still no different in weight from those of the normal fetus, but yet, in the 24-40th weeks they show advanced atrophy and weigh five to seven times less than normal. At the same time, in the 17th week, the thymus gland of the anencephalus already weighs twice as much as the normal and this ratio is preserved until the 31st-32nd week. Subsequently, however, the difference evens itself out and by the 8-9th week before birth the weights of the thymus gland in both the normal fetus and the anencephalus are almost the same.

Thus, an analysis of our data allows us to presume that the control exercised by the hypothalamo-hypophysial system over the adrenal function differs from the control over-all the other endocrine glands. Between the 17-24th weeks, a period sets in during which the functioning of the hypothalamo-hypophysial system is necessary for the normal development of the adrenals; its failure leads to a sharp atrophy of the adrenals and the susceptibility of the glands to this defect lasts throughout the whole of embryogenesis. It may be that the period between the

17-24th weeks, when the hypothalamo-hypophysial connections are being established in the normal development of the human fetus, a considerable increase in the secretion of corticoids sets in towards the 21st week of development, as is indicated by the results of a study of the phosphatases in the intestinal epithelium given above.

It is not yet known if this is connected with the beginning of the secretion of ACTH. The appearance of a small amount of ACTH has been described in eight fetuses examined during the 16-27th weeks of development [11] and it is also known that the administration of ACTH for 18 days to the newly-born anencephalus is attended by a normalization of the weights of the adrenals [7]. In laboratory rodents, atrophy of the adrenals in the fetus appears to be an inevitable and gradual result of decapitation.

From the point of view of endocrine relations in the adult organism, the absence of atrophy in the rest of the glands in the anencephalus and even the appearance of signs of hypertrophy (increase in gland weight) seems to be puzzling. The impression is obtained that some kind of hormone activity, normally affecting the development of the organs of the endocrine system apart from the adrenals is absent in the anencephalus. At the present time it is difficult to know whether these retarding effects arise in the adrenals, the function of which is very poor in the anencephalus. However, as indicated above, hypertrophy of the thymus gland in the anencephalus has already taken place by the 17th week, but towards the 30th week of development the gland shrinks considerably while, a month later it seems, the adrenals begin to suffer from the effects of the failure of the hypothalamo-hypophysial control and are not properly adjusted until the time of birth. Thus, no direct relationship between the development of the endocrine glands and adrenal functioning has been found.

The absence of correlation between the adrenals and thymus gland during normal embryogenesis up to the time of birth is not surprising if Peer's data [9] on the late (in the first days of postnatal life) maturation of the immunobiological (protective) system are taken into account.

SUMMARY

In order to determine the correlations between the activities of the thymus and adrenal glands, a study of the periods of hormone activity was made on 155 fetuses, 9-40 weeks old. The activity of alkaline phosphatases in the intestinal epithelium of the fetus served as a test of the corticoid level in the fetal blood.

Small amounts of corticoids appeared in the fetal blood for the first time after the 11-13th week, the amount practically increasing to the 20th week. From the 21-40th weeks, i.e., just before birth, the corticoid content of the blood in both series reached considerable proportions.

There is no correlation between the development of the thymus gland and the appearance of corticoids in the fetal blood.

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