THE EFFECT OF THYROID- AND PARATHYROIDECTOMY ON THE DEVELOPMENT OF THE FIRST, SECOND AND THIRD GENERATIONS

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L. I. Gromov and G. I. Plakutina

Thanatological Department (Head – Professor L. I. Gromov), Institute of Forensic Medicine (Director – Professor V. I. Prozorovskii) Ministry of Sanitation SSSR, Moscow
(Presented by Active Member N. N. Zhukov-Verezhnikov AMN SSSR)
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In the literature of recent years much attention has been paid to the functional relationship between mother and offspring. This relationship shows up very distinctly in the pathology of pregnancy and in the inadequate functioning of individual organs or systems in the mother [1-3, 5-8].

In a few experimental works on the removal of the thyroid and parathyroid glands the effects of thyroid- and parathyroidectomy in the parents on the progeny have been studied over a number of generations. One experiment in particular, with this aim in view, was carried out by Irie [9] who maintained observations on the progeny of rabbits over three generations after the thyroid glands of the parents had been removed for a number of generations.

An inadequacy in the functioning of one or other organ in the mother can be the cause of a premature functioning of the organs in the offspring [4].

Some experiments which we carried out at an earlier period on the removal of the suprarenals, hypophysis and thyroid gland from animals showed that, in a number of instances, there was an increased activity of the corresponding glands in the progeny which brought about persistent irregularities in development during the postembryonic period.

The aim of the present work was to demonstrate how a premature functioning of the glands of the fetus, caused by the removal of the thyroid and parathyroid glands from the mother, develops during the postembryonic period and in subsequent generations.

EXPERIMENTAL METHOD

Four hundred and sixty-eight white rats were kept under observation.

Two series of experiments were carried out: I, controls, consisted of experiments on ten animals, three to four months old and weighing between 195-210 g, and on the progeny from the various families (130 rats); II, a series of ten rats operated on at different periods during pregnancy and a series of four operated on before pregnancy. A control to determine the extent of gland removal was carried out by means of anatomical and histological examination of dead and killed animals. The weight of the experimental animals before fertilization by the males agreed with the weight of the rats from the control experiments. The progeny from the operated rats was followed up for three generations (P_1 – 139 rats, P_2 – 103 rats and P_3 – 67 rats).

The operated rats in the II series of experiments were paired with nonoperated males from the control series. In the first, second and third generations the animals were allowed to breed among themselves without any controlled pairing among relations.

The rats in all the experimental groups and their progeny were maintained under ordinary conditions. Constant observations were made on behavior, changes in weight, the course of pregnancy, the numbers of offspring, fertility, length of life, etc.

The Effect of Thyroidparathyroidectomy on the Development of the Progeny of the First, Second and Third Generations

Animal group	Number of young rats	Average fertility of mother	Survival rate (%)	Weight (g) after birth						Day on which postembryonic development took place		
				1st day	10th day	15th day	20th day	30th day	60th day	loosening of ear	cutting of teeth	opening of eyes
Controls	130	6.4	99.2	5.2	17.5	25.7	31.2	51.3	126.8	3-4th	8-10th	15-15th
First generation	139	6.3	28.0	4.2	14.4	18.2	22.3	43.6	108.0	1-5th	7-10th	13-20th
Second generation	103	8.4	91.2	5.1	16.1	21.4	27.3	40.7	111.0	3-4th	8-9th	14-19th
Third generation	67	8.3	97.0	5.0	15.4	19.1	26.0	45.0	113.0	5-7th	7-9th	15-18th

Some of the progeny were killed at definite periods of postembryonic development for anatomical and histological examination, others being left for further rearing. Individual observations were made on each animal. Material for histological examination was taken from the mothers and the progeny in each generation. Histological examination of the fetus, of the newly born rats and of rats five to six days old was carried out by total serial sectioning. The material was embedded in celloidin and paraffin wax and the sections stained in haematoxylin-eosin. Upwards of 5000 preparations were examined.

EXPERIMENTAL RESULTS

In a number of instances during the postembryonic period of development of the progeny from the first generation the thyroid gland had enlarged considerably, but in other instances this effect was not observed. It was shown that the degree of functional activity of the glands in the progeny of the first generation depended on the endocrine profile of the mother which changed from one pregnancy to another.

The extent to which the glands had been removed had a great effect on fertilization and on the rearing of the progeny in the operated rats. Rats from which the thyroid and parathyroid glands had been completely removed at the time of pregnancy gave birth to young but no further progeny were reared. Reimpregnated rats with partial removal of the thyroid and complete removal of the parathyroid glands became pregnant and reared their progeny (up to five pregnancies).

The length of life of operated rats after complete removal of the glands fluctuated from ten to eighty-four days after the operation: following partial removal it was 32 days to one year.

Atrophy of the thymus gland, hypertrophy of the hypophysis, enlargement of the liver and paresis of the stomach and intestines were observed in rats which had had the glands completely removed and which died soon after pregnancy. Operated rats, dying after the third or fourth pregnancy, were characterized by severe emaciation (25-30% loss of weight), a reduction in the dimensions of the liver, pancreas and ovaries, complete atrophy of the thymus and enlarged lymphatic nodules.

The change in the endocrine profile of the mother from one pregnancy to another had a considerable effect on the development of the fetus and young rats. Malfunction of the endocrine system in the mother brought about the death of the progeny during the intra-uterine period, premature births, edema, pug-like young, stillbirths and a high percentage of deaths on the first day of life. It should be noted that a factor such as stillbirths shows a considerable fluctuation depending on the serial number of the family. The maximum mortality was observed at the time when the families were undergoing operative interference. Taking all the families into account, the mortality at birth among the progeny in the first generation and during the first days of life amounted to 59%.

The dynamics of the changes in weight with age served as one of the indicators of postnatal development in young rats. The average weight of newly born rats in the control series of experiments amounted to 4.9 g; in the progeny of the first generation it was 4.2 g (from 3.2-7.6 g). The weight indices of newly born rats in the first generation were lower than those of the control animals, although this difference is levelled out by the fact that instances of dwarfness and gigantism among the litters were recorded at the

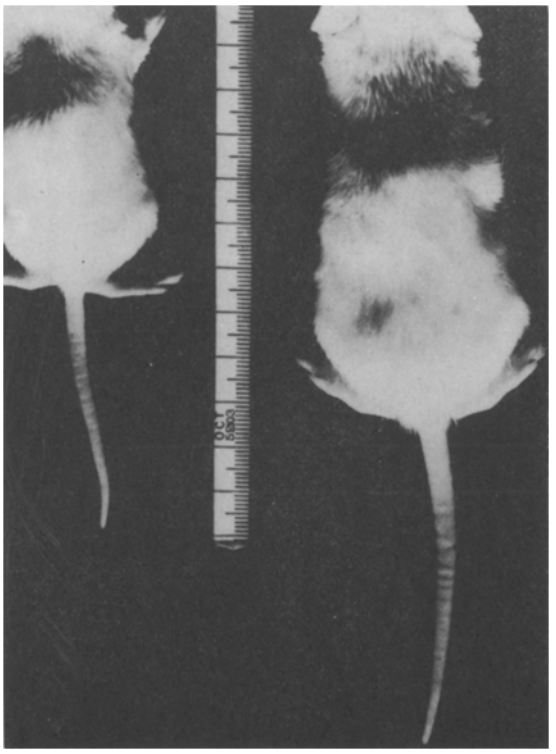

Fig. 1. Beadiness of the tail and the lagging behind in growth of young rats of the third generation brought about by removal of the thyroid and parathyroid glands from the great grandmother.

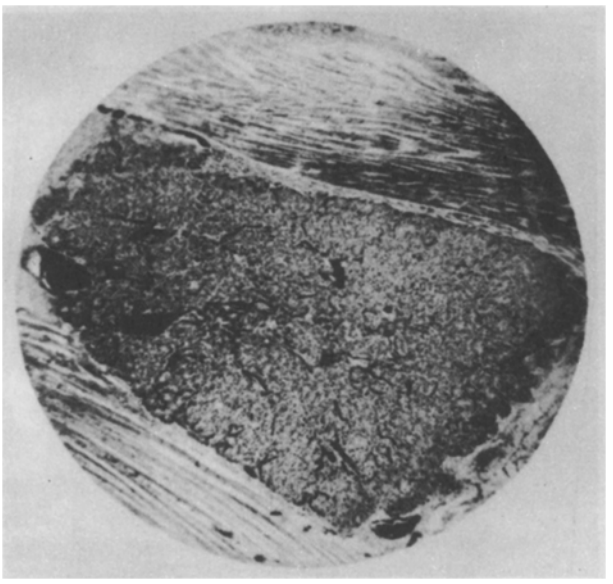

Fig. 2. Thyroid gland of a newly born rat from the progeny of nonoperated rats. Microphotograph. Stained with hematoxylin-eosin. Oc. 3x, Obj. 10.

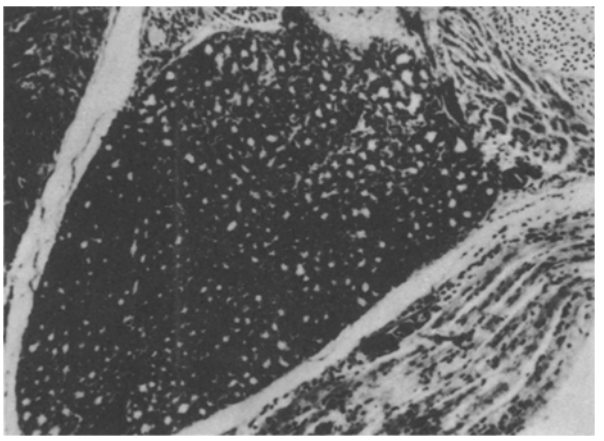

Fig. 3. Thyroid gland of newly born rat from the progeny of thyroidparathyroidectomized rats. Microphotograph. Stained with haematoxylin-eosin. Oc. 3x, Obj. 10.

same time. Small litters, dwarfness, large fetuses reaching gigantism, wasting of the skeleton, sparse fleecy coat and sterility were defects which developed to an extent of 24% in the first generation.

Such phases of development as loosening of the ears, cutting of the teeth and opening of the eyes were subject to sharp fluctuations both in the direction of prematureness and of retardation (see table).

Besides the features enumerated, an imperfect functioning of the endocrine system of the parents led to constitutional disturbances in the progeny (sons, grandsons, great grandsons) which took the form of a wasting of the skeleton, changes in the bone extremities and defects of growth. Female rats of the first generation, reaching sexual maturity, retained these defects of development throughout their lives, but their sexual functions were not affected. Disturbances in the reproductive functions of the males, reaching as far as sterility, were noticed.

In the second and third generations fertility was high and pathological deviations in the reproductive functions of males and females were not observed.

The progeny of the second generation at birth was large and normally developed. However, in a number of instances towards the 20th-30th day of life there was a lag in growth and in weight increment. The young rats were narrow-headed, sickly, of frail constitution and timid. Instances of dwarfness and a lagging behind in growth were recorded in those litters in which males, descended from small liters, participated. This feature is interesting from the point of view of the hereditary transmission of growth defects from the father. However, in the grandsons of thyroidparathyroidectomized rats, anomalies in development appeared, but were fewer in comparison with those in the first generation (11-13%).

Disturbances in the calcium metabolism, caused by extirpation of the parathyroid glands in the parents, were most frequently associated with anomalies in skeletal development. Among individuals of the third generation, together with the appearance of defects of development characteristic of the first and second generations, a new feature developed in the form of a beaded tail (Fig. 1). X-ray examination showed that the change in the external appearance of the tail was connected with osteoporosis and a breakup of the fibers in the cortical layer of the tail vertebrae.

An examination of the internal secretion glands of newly born rats from different generations revealed wide, individual deviations within the limits of both a single litter and of a whole generation. The fetus reacts to an imperfect balance in the endocrine system of the mother by an increase in the function of analogous or other glands.

On the first day after the birth of young rats from operated mothers (P_1), hypertrophy and congestion of the thyroid and parathyroid glands was noticed (an increase in volume of 2-2½ times compared with the controls).

The morphological appearance of the thyroid gland was evidence for the gland's increased activity as far as the third generation. Compared with the controls, the thyroid glands of one day old, living rats were distinguished by a differentiation in the follicles developed along the periphery and in the center of the gland. The follicles were

distinctly isolated from one another. The epithelial cells of the follicle were tall, cubical and cylindrical. The nuclei were large and characterized by having a basal disposition. The follicles were exposed, with or without clear colloid. Mitoses were met with more often that in the controls (Figs. 2 and 3).

An increase in the absolute and comparative weights of the thyroid glands was noticed in rats of the second and third generations taken for histological examination when 3-4 months old. As a rule, the parathyroid glands were larger than those in the controls.

The data obtained show that an augmented functional background of the thyroid and parathyroid glands, appearing in the progeny of the first generation, was maintained in the second and third generations.

Thus, the changes brought about in the fetus by an insufficiency of certain of the endocrine glands in the mother are reflected not only in the embryonic and postembryonic periods of the development of the individual but also on the following generations.

SUMMARY

The effect produced by thyroparathyroidectomy on the development of the progeny in three generations of rats was studied.

Thyroparathyroidectomy in mothers caused anomalies of fetal development, incompatible with life, or gave use to premature function of the thyroid gland. During the first days after birth in young rats born of operated mothers there was hypertrophy and congestion of the thyroid and parathyroid glands (2-2½ fold enlargement as compared with control).

Morpho-histological examination of the thyroid gland pointed to an increased function. An augmented function of the thyroid and parathyroid glands occurring in the progeny of the first generation was retained in the second and third generations.

Insufficiency of the endocrine system of ancestors induced constitutional disturbances in the progency in the form of gigantism, dwarfism and sterility. Developmental defects were manifested by changes in the skeleton and disturbances of the skin and fur.

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