

THE INFLUENCE OF THE SUPRARENAL GLAND ON THE THYMUS.

III. STIMULATION OF THE GROWTH OF THE THYMUS GLAND FOLLOWING DOUBLE SUPRARENALECTOMY IN YOUNG RATS.

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PLATE 32.

(Received for publication, July 23, 1924.)

It has been shown that double suprarenalectomy, in the rat and rabbit, if carried out after thymus involution had normally begun, brought about regeneration of the thymus gland (1-3). We pointed out that the regeneration probably began very soon after suprarenal ablation; that it was detectable early and progressed rapidly; and that it was completed in the rat in most cases within 2 weeks. These observations concerning thymus regeneration in older animals prompted us to study the effects of suprarenalectomy on the thymus glands of growing rats. We, therefore, suprarenalectomized animals the age of which varied between 35 and 54 days. The thymus of a normal rat increases progressively in weight and generally reaches its maximum size between the 80th and 90th days of life, and thereafter shows a gradual absolute decrease (4, 5).

We have been unable to find literature specifically concerned with experiments along these lines.

Methods.

All rats were reared in the laboratory from very tame albino stock (*Mus norvegicus albinus*), the original animals coming from the Wistar Institute. In our first paper we described the methods used in the care of our animals, the operative technique,¹ and the usual postoperative treatment. Autopsies were performed on all animals and a careful search made for suprarenal tissue. The thymus glands were removed as soon after death as possible and were dissected clean of the

¹ All operations were performed under ether anesthesia.

surrounding fat, connective tissue, and lymph nodes, and weighed. They were fixed in 10 per cent formalin, embedded in paraffin, and stained with hematoxylin and eosin.

We should like to emphasize again that our control and experimental rats were kept under identical laboratory and nutritional conditions at all times, and that standardization of these factors is extremely important in any research involving the thymus gland, as this gland is subject to considerable variation dependent upon these influences.

EXPERIMENTAL DATA.

The material includes a study of thirty-nine young rats, twenty-five of which were suprarenalectomized. Of these twenty-five, eleven died from 1 to 41 days after suprarenal extirpation, and were excluded from the experiments proper. The remaining fourteen animals were sacrificed at 2 week intervals from 2 to 8 weeks after operation, and the important data concerning them and their controls are summarized in the table. Of the fourteen control rats, eleven were litter mates of the operated animals.

The thymus gland of each of the fourteen suprarenalectomized rats, was heavier than that of its respective control, the difference varying from 12 to 85 per cent. The average thymic weight of the fourteen suprarenalectomized rats was 49 per cent greater than that of the control animals. On the other hand, if these weights are compared with Donaldson's standards of normal, we find that the average weight of the thymuses of the suprarenalectomized rats was 68 per cent above the normal, while that of the control rats was 12 per cent, making the difference between the average thymic weights of the suprarenalectomized and control animals + 56 per cent (6).

Concerning the eleven suprarenalectomized animals which died during the course of these experiments, and which were excluded from the calculations, three died within the 1st week after operation from acute postoperative effects; one died during the 2nd, and another during the 3rd week from suprarenal insufficiency; while six others died between the 4th and 6th weeks after operation. Although we pointed out previously that snuffles and progressive suprarenal insufficiency do not necessarily prevent regeneration of involuted thymus glands, we excluded these eleven rats because we wanted to avoid the complicating effects of these two conditions on the growing animals,

TABLE I.

| Rat No. | Sex. | Length of time after suprenalectomy. | Age at death. | Weight at death. | Major cause of death. | Weight of thymus. | Difference between thymuses of suprarenal- ectomized and control rats. |
|---------|------|---|------------------|------------------------|--------------------------|-------------------------|--|
| | | <i>days</i> | <i>days</i> | <i>gm.</i> | | <i>gm.</i> | <i>per cent</i> |
| R 39-3 | M. | 11 | 49 | 80 | Back broken. | 0.400 | +81 |
| R 42-1 | " | Age control. | 50 | 110 | Sacrificed. | 0.220 | |
| R 46-2 | F. | 15 | 68 | 166 | " | 0.530 | +80 |
| R 48-2 | " | Litter control. | 68 | 150 | " | 0.293 | |
| R 46-3 | " | 15 | 68 | 145 | " | 0.366 | +26 |
| R 48-4 | " | Litter control. | 68 | 120 | " | 0.290 | |
| R 46-4 | M. | 15 | 68 | 185 | " | 0.635 | +70 |
| R 48-3 | " | Litter control. | 68 | 175 | " | 0.374 | |
| R 37-4 | F. | 29 | 64 | 167 | " | 0.476 | +54 |
| R 40-1 | " | Litter control. | 64 | 123 | " | 0.308 | |
| R 38-1 | " | 29 | 70 | 163 | " | 0.415 | +60 |
| R 40-2 | M. | Litter control. | 70 | 168 | " | 0.260 | |
| R 39-1 | " | 29 | 70 | 163 | " | 0.369 | +12 |
| R 40-3 | " | Litter control. | 70 | 161 | " | 0.328 | |
| R 38-3 | F. | 30 | 71 | 130 | " | 0.378 | +55 |
| R 41-2 | M. | Age control. | 70 | 155 | " | 0.243 | |
| R 43-1 | F. | 31 | 77 | 143 | " | 0.418 | +44 |
| R 44-4 | " | Litter control. | 77 | 156 | " | 0.295 | |
| R 44-3 | " | 31 | 74 | 145 | " | 0.479 | +12 |
| R 50-1 | " | Litter control. | 74 | 170 | " | 0.426 | |
| R 47-1 | " | 41 | 86 | 160 | " | 0.312 | +35 |
| R 49-2 | " | Litter control. | 86 | 165 | " | 0.231 | |
| R 44-2 | " | 55 | 98 | 210 | " | 0.552 | +85 |
| R 49-4 | M. | Litter control. | 98 | 255 | " | 0.298 | |
| R 44-1 | F. | 55 | 98 | 150 | " | 0.375 | +39 |
| R 45-3 | " | Litter control. | 98 | 167 | " | 0.271 | |
| R 43-2 | " | 55 | 101 | 152 | " | 0.392 | +34 |
| R 37-2 | M. | Age control. | 104 | 240 | " | 0.292 | |

since they would be reflected also on the growing thymus. It is noteworthy, however, that, in spite of the fact that some of the rats which died were extremely ill for 2 or 3 weeks, their thymuses were heavier than those of the Wistar rats of the same age.

Young rats withstand the late effects of suprarenal ablation much more poorly than do older animals. This is due to their greater susceptibility to intercurrent infections. Almost every surviving suprarenalectomized animal developed snuffles, and this undoubtedly contributed to the death of many. The number of deaths would probably have been much greater had we not sacrificed the animals at the scheduled time of 2, 4, 6, and 8 weeks after suprarenalectomy irrespective of their clinical condition. Among our control rats there was only one instance of severe snuffles, despite the circumstance that the control and operated animals were frequently kept in the same cages, and always under the same environmental and nutritional conditions.

The figure shows thymuses of twelve rats, six of which had been suprarenalectomized. Their thymuses are compared with those of their controls.

Histology.

Microscopical examination discloses no remarkable difference between the thymuses of the suprarenalectomized and control rats. The lobules are divided into prominent cortical and medullary zones, and the lobules of the thymuses of the suprarenalectomized rats are on the whole larger than those of the control animals.

DISCUSSION.

The results show that suprarenalectomy, if carried out in young rats 35 to 54 days of age, is an additional stimulus to the growth of the thymus gland. The average thymic weight of a series of fourteen suprarenalectomized rats is about 50 per cent above that of the average weight of fourteen controls. This thymic hyperplasia is apparent soon after suprarenalectomy; the maximum effect being attained usually within 2 weeks. To our knowledge the only other controllable experimental condition which brings about such marked prepubertal thymic hyperplasia is castration, but castration is not so

powerful a stimulus (2, 7-9). Here again, we are confronted with further evidence of the similarity in reaction of the thymus and lymphoid tissue both to suprarenalectomy and gonadectomy.

Prepubertal thymic hyperplasia following suprarenalectomy may offer a partial explanation of the pathogenesis of status lymphaticus. In the human cases hypoplasia of the suprarenals is one of the outstanding pathological findings together with a large thymus and prominent lymph nodes (10-12). While earlier authors emphasize the hypoplastic changes of the chromaffin tissue, the later work of Marine and Baumann on the rabbit and our work on the rat clearly indicate that the lymphoid overgrowth is dependent upon interrenal and gonadal insufficiency.

Of additional interest in this connection is the fact that an extraordinary degenerative change takes place in the suprarenal cortex of infants during the first month of life, these changes having been independently described by Thomas, Elliott and Armour, and Kern in 1911 (13-15). Their papers were soon followed by the more extensive reports of Landau (16), and Lewis and Pappenheimer (17). The anatomical descriptions of the above mentioned observers agree as regards the essential lesions. The degeneration is fully established at the end of the 2nd week of life and during the next 5 or 6 weeks rapid removal of the broken down cells takes place leaving the relatively thin glomerular layer intact. This layer collapses upon the medulla, and, according to Lewis and Pappenheimer, there is no appreciable increase in width of the cortex, that is, to say regeneration, up to the age of 3 years. The cause of this cortical destruction is not definitely known. Marine, Lowe, and Cipra (18) found that during the 2nd week of life in infants there is a rise in heat production, which they attributed to the involution of the suprarenal cortex on the basis of previous heat production studies on suprarenalectomized rabbits.

We are of the belief that the pathogenesis of the lymphoid state may be connected with excessive spontaneous cortical involution in infancy, or with a disturbance in the normal regeneration of the suprarenal gland following this spontaneous involution. It is conceivable that abnormal spontaneous involutions in infancy may lead to the production of hypoplastic suprarenals.

Hemicephaly is associated with high grade aplasia of the suprarenals and usually in addition presents a large thymus (14, 19-23). With regard to the suprarenal itself, most writers state that the aplasia concerns the medulla and cortex equally. Thus the suprarenal glands are abnormally small both in status lymphaticus and in hemicephaly, and in both enlargement of the thymus is present, which enlargement may stand, in regard to the suprarenals, in the relation of cause and effect.

CONCLUSIONS.

1. Double suprarenalectomy in growing rats is an additional stimulus for thymic growth and brings about marked prepubertal hyperplasia of this gland.

2. Our results on young rats suggest that the suprarenal cortex may be a factor in the excessive thymic hyperplasias seen in infants and children.

I wish to express my appreciation for the helpful and suggestive criticism of Dr. David Marine.

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EXPLANATION OF PLATE 32.

FIG. 1. Showing thymuses of young suprarenalectomized rats compared with their controls.

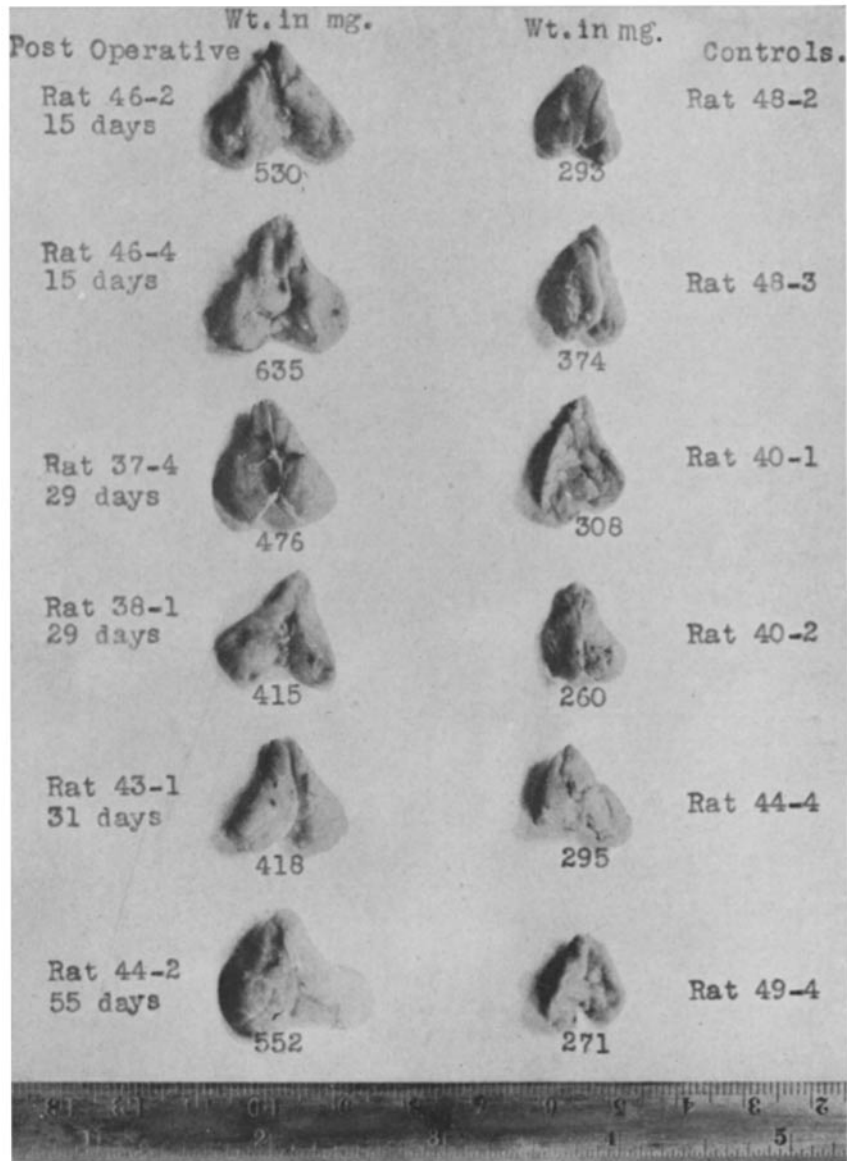


FIG. 1.

(Jaffe: Influence of suprarenal gland on thymus. III.)