THYMUS.*

By A. W. SPENCE, M.A., M.D. (Cantab.), M.R.C.P. (Lond.)

(Assistant Physician and Assistant Director of the Medical Unit, St. Bartholomew's Hospital, London.)

The thymus gland arises as a paired structure from the entoderm of the third and fourth branchial clefts, the anlagen from the fourth cleft, however, remaining rudimentary in most animals. The lobes of the thymus are made up of numerous follicles, which consist of a reticulum containing the thymic cells (lymphocytes), which are more closely packed in the outer or cortical part than in the inner or medullary. The medulla, but not the cortex, contains the Hassall's corpuscles, the origin of which is doubtful.

Involution.

It is generally agreed that the weight of the thymus increases up to the end of the second year of life, and that the organ begins to involute at puberty, when there is a rapid reduction for four or five years, after which reduction is more gradual. The diminution in size is due mainly to a decrease in the small thymic cells; new elements are being formed, however, during involution, but at a greatly reduced rate. Pathological involution occurs in a large number of generalized disease processes, such as acute and chronic infections, and also during pregnancy and in malnutrition. Such an involution is extremely rapid, and is brought about by the ingestion of the small thymic cells by the reticular cells. Regeneration takes place rapidly after recovery from the causative condition.

The cause of involution is unknown, but it is probably due to a complicated interaction of the various endocrine glands. In young rabbits, Marine and his associates⁽¹⁾ have shown that thyroidectomy hastens and that castration delays involution of the thymus. Removal of the suprarenals not only prevents involution, but may cause regeneration of a thymus already involuted. Thyroidectomy prevents this, even after removal of both suprarenals and gonads. A study of the inter-relations of the thymus and suprarenals has been carried out by Selye⁽²⁾. He found that by subcutaneous injections of atropine, morphine and formaldehyde he could produce in 48 hours marked involution of the thymus in rats. This was accompanied by increase in the size of the suprarenals, attributed mainly to cortical hypertrophy. He was unable to produce thymic involution by these agents in adrenalectomized rats, and concluded that an adrenal secretion was essential for such involution. He showed that this secretion was neither adrena-line nor cortical hormone.

Physiology.

The function of the thymus is still a matter of conjecture in spite of the large amount of experimental research that has been done on the subject. In the light

* A Post-Graduate Lecture delivered under auspices of The Fellowship of Medicine at The National Temperance Hospital on December 11th, 1936.

of recent work it appears to play some part in growth. As with other endocrine glands the problem has been tackled by determining the effect on the organism of removal of the gland and of the administration of extracts.

Thymectomy. The results of thymectomy have been contradictory and a good deal of the work is unreliable. Some of the earlier observers reported rachitic changes in young thymectomized rats, but subsequent investigators have found no evidence in support of this. In a series of careful experiments on dogs Park and McClure⁽³⁾ concluded that the thymus is not essential to life in the dog, and that its removal produces no detectable change in the animal, except perhaps some retardation in development and in closure of the epiphyses. From experiments on thymectomy in hens it was thought that the thymus was concerned in the normal metabolism of calcium, as such animals laid eggs with imperfectly calcified shells. This, however, has recently been contradicted, the suggestion being made that the changes were possibly brought about through damage to the parathyroids. Damage to the parathyroids may also be responsible for the osteoporosis and deficient callus formation in experimental fractures that have been reported in thymectomized animals.

Very recently the effect of thymectomy in successive generations of rats has been studied⁽⁴⁾. Thymectomy performed on young rats from 17 to 24 days old produced no recognizable change in their growth and development, but in the offspring of the thymectomized animals a definite retardation in growth took place, an effect which was constantly observed only during the first six weeks of life, subsequent growth being normal.

Thymic Extracts. The early work on the effect of feeding thymus and of the injection of thymic extracts yielded little information of value. It was not until 1930 that a definite advance was made, when Asher obtained an aqueous extract of thymus ("thymocrescin") which accelerated the growth of rats. Recently Rowntree, Clark and Hanson⁽⁵⁾ treated successive generations of rats with daily intraperitoneal injections of thymic extract, the treatment of the young beginning from the age of 16 to 20 days. The extract increased the fertility of the parent rats, and accelerated the rate of growth and development of the offspring. The effects were greater in each succeeding generation under treatment. Growth was affected only in the early days of life and gigantism was not produced. Psychic precocity was as marked as the physical: thus fifth generation test animals could be weaned at three days of age.

Pathology.

There is no known disease entity in which the thymus occupies the causal rôle. Hyperplasia of the thymus occurs in toxic goitre, Addison's disease, acromegaly, myasthenia gravis, and occasionally in endemic goitre and idiopathic epilepsy, but the reason for such a change is unknown. The thymus may or may not be enlarged in status lymphaticus, which is defined by Marine⁽⁶⁾ as a constitutional defect associated with a lowered resistance or increased susceptibility to a great variety of non-specific, physical and chemical agents. Young and Turnbull, together with a committee of the Medical Research Council⁽⁷⁾, concluded, after an investigation into the size of the thymus in deaths from all causes,

including those in which no obvious cause of death was found post-mortem, that an abnormally large thymus in itself is not indicative of status lymphaticus and that the so-called status thymico-lymphaticus is not a pathological entity. A number of those, however, who consider status lymphaticus to be a pathological entity, hold that it is of secondary importance whether the thymus be large or small, as it only indicates the degree of lymphoid reaction at the time of death. Death in status lymphaticus does not depend on the size of the thymus, the degree of lymphoid hyperplasia or the degree of arterial hypoplasia, but on a peculiar susceptibility of the organism. The term "thymic death" is a misnomer.

Tumours of the thymus are usually unassociated with general bodily disturbances, such as are often encountered in tumour formation in other ductless glands. The cases of a pluriglandular syndrome associated with primary carcinoma of the thymus are exceptional.

On the basis of reports of osteoporosis and deficient callus formation in experimental fractures in thymectomized animals, Secord, Wilder and Henderson⁽⁸⁾ treated a case of osteogenesis imperfecta with an extract of thymus. The patient was a boy, aged 13, who since the age of 5 had had multiple fractures, and an X-ray examination of the skeleton showed marked generalized osteoporosis. After daily injections of extract for three months, he was seen six months later and was found to have had no further fractures. X-ray examination showed marked improvement in the density of the femora, but no significant changes in the spine and ribs. The case is of interest in that it suggests an endocrine disturbance in this rare disease, but further research is necessary before any definite statement can be made.

Although our knowledge of the thymus at the present time is scanty, recent work, which however needs confirmation, suggests that we may be about to obtain some surer information concerning its function.

REFERENCES.

- (1) Marine, D., Manley, O. T. and Baumann, E. J., *Jour. Exper. Med.*, 1924, xi, 429.
- (2) Seyle, H., *Brit. Jour. Exper. Path.*, 1936, xvii, 234.
- (3) Park, E. A. and McClure, R. D., *Amer. Jour. Dis. Child.*, 1919, xviii, 317.
- (4) Einhorn, N. H. and Rowntree, L. G., *Endocrin.*, 1936, xx, 342.
- (5) Rowntree, L. G., Clarke, J. W. and Hanson, A. M., *Arch. Int. Med.*, 1935, lvi, 1.
- (6) Marine, D., *Arch. Path.*, 1928, v, 661.
- (7) Young, M. and Turnbull, H. M., *Jour. Path. Bact.*, 1931, xxxiv, 213.
- (8) Secord, E. W., Wilder, R. M. and Henderson, M. S., *Proc. Staff Meetings Mayo Clinic*, 1936, xi, 1.