From the literature relating to the reactions of the endocrine organs in low environmental temperature it is apparent that the thyroid and adrenal glands take part in the chemical regulation of heat. A rise in their secretory activity contributes substantially to bringing about and maintaining an accelerated rate of metabolism when the body is exposed to cold.

The increased function of the thyroid can be morphologically registered with great exactitude, and hence valuable possibilities have been obtained of studying the function of this organ. As the thyroid and adrenals are dependent on the pituitary body for the maintenance of their normal functional state, the pituitary is essential for their reactions under cold conditions. From this it does not follow that the pituitary actively stimulates these organs to increased hormone production, although this assumption has been used as a working hypothesis in some investigations so far as the thyroid is concerned. An increased production of thyrotropic hormone in response to the cold stimulus, however, has not been previously demonstrated, and the increased thyroid activity may have been elicited by other, overlooked factors. It has, for example, been experimentally shown that a raised blood pressure may constitute such a factor. So far, it has not been possible to draw conclusions respecting the functional action of the pituitary on the thyroid on the basis of micromorphological analyses of the anterior pituitary lobe. Certainly significant reactions arise in the basophilic cells under experimental conditions in which the organism can be expected to make demands for increased thyroid activity, but these conditions, e.g. when thyroid tissue has been excised and when the synthesis of thyroid hormone has been disturbed, may be regarded as forms of injury. On this account the basophilic-cell reactions do not allow of any conclusion respecting hormone production, for morphologically similar changes arise after quite a number of different forms of injury. Nor have hormone analyses undertaken after thyroidectomy of the animals brought clarity to the question whether any connexion exists between structural and hormonal changes. The aim of the present investigation has been to study the structural and hormonal reaction of the pituitary in its relation to the thyroid gland after exposure of the experimental animal to a low temperature so chosen that injuries will not arise.

As the experimental results obtained have been presented in the form of summaries at the end of each of the chapters 4–9, they are only reproduced here in synoptical form. Rats which had for several weeks been kept in a low environmental temperature of either +5°C to +10°C or +1.5°C to 3°C, have not shown any deterioration in their condition during the period of the test. A careful search has been made for signs of injuries, but none have been detected. In these rats a significant decrease in weight of the pituitary occurs. With statistical certainty the anterior lobe as well as the intermediate lobe diminishes in weight, while the size of the posterior lobe remains unaltered.

After the exposure to cold a distinct rise in function has occurred in the thyroid gland, as was expected. Therefore, the organism can be said to have made a demand for increased thyroid
activity. In the pituitary the basophilic cells hypertrophize, and scattered groups of these enlarged cells can be observed. Further, vacuola-tion takes place in the basophilic cells to a greater extent than normally. The changes mentioned are most pronounced in males. Similar changes arise after thyroidectomy, when the organism can also be expected to make increased demands for thyroid activity. From a micromorphological point of view the changes in the basophilic cells after cold exposure and thyroidectomy have been found to be identical. This identity would seem to be founded in fact, since the vacuolation that is associated both with thyroidectomy and cold exposure can be precluded by administration of small doses of thyroxine.

It has been considered that the reactions of the basophilic cells to cold can be investigated under more constant experimental conditions if these cells are not exposed to the influence of the increased incretion of thyroid hormone by the organism itself. For this reason thyroidectomized rats treated with a constant daily substitution dose of thyroxine have been used. The dose employed has been that which prevents thyroidectomy cells from arising in thyroprivic rats kept at a temperature of + 25°–+ 28° C, and this dose, which has been adjusted to the body area, has varied between 6 $\gamma$ and 12 $\gamma$ per day. A comparison between cold-exposed rats treated in this way and rats not exposed to cold showed that in the former a statistically significant increase in the number of the basophilic cells had taken place.

The changes in the basophilic cells of the pituitary probably represent a cell-work in the course of which a consumption of the cellular material takes place. This consumption can be observed by the occurrence of degenerating basophiles, while at the same time new ones are being formed. The significant decrease in size of the anterior lobe may no doubt be regarded as a result of these cellular processes. Hence the changes seem to be analogous with those that were observed in the pituitaries of castrated female rats, where the basophilic cells re-form and degenerate at the same time as an increased production of gonadotropic hormone occurs (Brolin and Theander, 1944). Hormone analyses and morphological analyses have been carried out on the same rats, and the results obtained can therefore be put in relation with each other with less risk of error. The occurrence of thyrotropic hormone has been studied both in serum and urine extract with the use of day-old chicks as test-animals. Rat serum in a dose of 1 ml. per day for 5 days did not have any non-specific action on the thyroid glands of the chicks. Injections of serum from control rats kept at a temperature of + 25°–+ 28° C. was found, on comparison with untreated chicks, not to have brought about any increase in the height of the acinar epithelium. The occurrence of thyrotropic hormone, however, was determined in the serum from cold-exposed rats as a significant increase in epithelial height had been registered. The increased thyroid activity in response to cold was thus caused by an increased production of thyrotropic hormone. At the test with urine extract the thyroids of the test chicks were judged according to the method of Heyl and Läqueur (1934). The result suggests that in cold-exposed rats thyrotropic hormone is excreted into the urine.

A raised production of thyrotropic hormone presupposes increased cellular work, which is probably represented by the reactions of the basophilic cells in response to the cold stimulus. Identical reactions arise in the basophiles when, after thyroid-ectomy, the organism likewise makes demands for an increased thyroid function. In consonance with this, thyroxine treatment counteracts the reactions of the basophilic cells. Moreover, it has been possible to establish that an increased thyrotropic hormone production takes place in cold-exposed rats that have exhibited
the cell changes in question. There are, thus, very strong reasons for the conclusion that thyrotropic hormone is produced in the basophilic cells of the anterior pituitary. Increased activity in the thyroid gland after the cold exposure can thus be fitted into a chain of physiological mechanisms composed of four distinct links, viz. the cellular reactions of the anterior lobe, incretion of thyrotropic hormone, cellular reactions of the thyroid gland, incretion of thyroid hormone.

The influence of various factors on the cellular reactions of the anterior pituitary has been investigated, at the same time as the functional state of the thyroid has been taken into account. Thyroxine reduces the activity of the thyroid under cold conditions, this action being probably transmitted by the basophilic cells of the pituitary. It is still an open question whether this action is direct, humoral, or indirect, e.g., via the hypothalamus. The sympathetic innervation of the pituitary is not of essential importance for the production of thyrotropic hormone. This result is in agreement with the previous finding that the thyroid also reacts to the cold stimulus after bilateral extirpation of the cervical sympathetic (Uotila, 1939).

The anterior pituitary lobe does not raise its production of thyrotropic hormone under cold conditions, and there is no baso-

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philic-cell response to these conditions if the hypophyseal stalk connexion with the hypothalamus has been completely severed.

In opposition to what has hitherto been considered to be the case, stalk transection has constantly given rise to distinct changes in the thyroid of the rat, the thyroid picture becoming, irrespective of any temperature tests, considerably less active than in the non-operated control rats. This observation has been made in so large a number of cases that it cannot depend upon chance. The mortality associated with the cold exposure of stalk-cut rats has been high, which probably depends on the fact that their regulation of body heat has been defective. However, some of them have endured a severer cold exposure than hypophysectomized rats are stated to be able to stand. Transection of the stalk connexion, therefore, does not seem entirely to eliminate the hormonal influence of the pituitary in a metabolic respect.

Stalk transection causes a reduction in the gonadotropic function of the pituitary in male rats, so that degenerative changes arise in the germinal epithelium. Testicles, seminal vesicles and prostate diminish in weight. This effect has been previously demonstrated by a number of investigators, but has been contested later by others. No influence from the cold exposure was observed on the gonadotropic function of the pituitary, which was also reduced in the females. In normal male rats, the exposure to cold brought about the reduced gonadotropic function. The cause of this seems to be that, in them, the basophilic cells were requisitioned to a larger extent for the production of thyrotropic hormone. In the females, whose basophilic-cell responses to cold were weaker, no diminution in the gonadotropic function could be detected.

The question whether adrenal hypertrophy following cold exposure depends on increased thyroid incretion has been made the subject of an investigation with the aid of thyroidectomized rats treated with thyroxine. The cold-exposed rats exhibited a significant increase in adrenal weight, although they were not given a higher substitution dose of thyroxine than the likewise thyroidectomized rats kept in a warmer environment. The enlargement of the adrenals under cold
conditions is therefore not caused by the influence of thyrotropic hormone on the thyroid and a thyroxine action following upon this. On account of this the possi-

bility is also actualized that an increased incretion of corticotrophic hormone also occurs in animals exposed to cold. In analogy with what has been pointed out respecting the thyrotropic hormone a direct demonstration of the corticotrophic hormone seems, however, to be necessary before such a hypothetic increase in production can be accepted as a fact.