As was mentioned in Chapter 7, increased thyroid activity in cold-exposed rats can be fitted into a chain of physiological mechanisms in which four links are distinguishable, viz. (a) cellular reactions of the anterior pituitary lobe, (b) incretion of thyro-tropic hormone, (c) cellular reactions of the thyroid gland, (d) incretion of thyroid hormone. On each of these links different factors may be conceived as acting. In the present investigation the factor represented by the work of the cells in the anterior pituitary lobe chiefly comes under discussion. This cell work is probably independent of the sympathetic innervation, as was shown in Chapter 7.

On the other hand, the connexion of the pituitary with the hypothalamus is essential for that cellular work which takes place in the production of thyrotropic hormone, as is evident from the experimental results submitted in Chapter 8. Against these results the criticism might be raised that the significance of the postoperative, ischaemic necrosis may have been underrated. To this it can be urged that this necrosis, which has never been directly observed but has merely left traces in the shape of small cicatrices of connective tissue, has probably not arisen as a result of direct damage to the pituitary. The transection of the stalk has taken place in front of the oral margin of the pituitary. The connective-tissue scars in question have invariably had the same localization, corresponding to the distribution of the vessels coming from the stalk in the immediate vicinity of their point of entry. A complete severance of the stalk therefore results in a connective-tissue cicatrix of this kind. In this connexion it may be pointed out that Westman, Jacobsohn and Hillarp (1943) severed the stalk connexion behind the oral border of the hypophysis, voluntarily sacrificing hypophyseal tissue. They showed that a genital atrophy arose in cases where a small amount of anterior lobe substance had been lost but the stalk connexion had been broken off, but that no such atrophy arose when the stalk connexion was left, while the amount of the anterior lobe tissue was greatly reduced. Probably the loss of tissue connected with the cicatrization does not play any decisive role. Finally, to an objection of the above-mentioned kind it may be pointed out that cytological analyses of the anterior lobe have shown that the decrease in the hormone production of this organ is referable to a reduced power of reactivity in the individual cells in question.

Thyroxine in small doses, as was shown in Chapter G, influence the cellular work of the pituitary, so that the production of thyro-tropic hormone diminishes. This action may be direct, i.e. humoral, but it may also be indirect. In the latter case an action via the hypothalamus and the stalk claims first attention as a possibility. Without sufficiently well-founded criteria for judging what happens when the thyroid gland is inactivated by thyroxine action (Uotila 1939) endeavoured to determine whether or not the thyroxine acted by way of the hypothalamus and stalk. He set out partly from the hypothesis that the thyroxine acted upon the thyrotropic incretion, partly from his earlier experimental finding (Uotila, 1939) that transection of the stalk did not cause any lowering of thyroid activity.
In support of the hypothesis that thyroxine influences the incretion of thyrotropic hormone he cited the results obtained by Kuschinsky (1931) as well as Hohlweg and Junkmann (1933), viz. that the thyrotropic hormone content of the pituitary diminishes after administration of thyroxine. To this the objection may be brought that it has not been shown that the amount of thyrotropic hormone stored in the pituitary has anything to do with the incretion. However, as already stated, the results obtained in the present investigation have shown that this hypothesis is correct. Uotila’s conclusion that thyroxine acts directly on the pituitary because administration of thyroxine reduces thyroid activity in stalk-cut rats is therefore not justifiable, for the thyroid activity of these rats diminishes without thyroxine treatment. As pointed out in Chapter 8, it can be assumed that the hypothalamic-hypophyseal junction has not been completely severed in the experiment cited. The question whether thyroxine acts directly on the pituitary or indirectly, in which latter case the hypothalamus seems to come in question in the first place, is therefore still open.

The work of the anterior pituitary cells that results in the production of thyrotropic hormone also seems to produce other results. The micromorphological analysis has shown, as mentioned in Chapter 4, that this cellular work finds expression in a hypertrophy of the basophilic cells, some of which show signs of increased activity while some degenerate. In Chapter 5 it was further shown that the basophiles increase in number. Probably a new formation as well as a consumption of these cells therefore takes place, similar to what is found to occur when the basophilic cells are called upon for the production of gonadotropic hormone (Brolin and Theander, 1945). The statistically verified diminution in size of the anterior lobe after cold exposure can no doubt be regarded as a consequence of a progressive consumption of the cell material. In the cellular work that can be assumed to be the cause of the increase in thyrotropic hormone production the basophilic cells are probably requisitioned to a great extent. This can be conceived as influencing the production of gonadotropic hormone, since the basophilic cells are probably also engaged in the manufacture of this hormone. As a matter of fact, that a reciprocal action of this nature can arise has been found likely in other connections. When an increase in the stored amount of gonadotropic hormone occurs in the pituitary of the castrate in conjunction with pronounced reactions in the basophilic cells, the stored amount of thyrotropic hormone is reduced (Chapter 1). It has likewise been mentioned that a decrease in the stored amount of gonadotropic hormone has been observed in the pituitary after thyroidectomy. In this case, too, the reactions of the basophilic cells are lively. At the examination of the gonads of the cold-exposed rats, as was stated in Chapter 4, other changes could be observed than a slight loss of weight of the testes, which might have depended upon chance. As was mentioned, no histological changes were found in the gonads. In the males, however, a statistically significant decrease in weight was registered for the seminal vesicles and prostate. A lowering of the incretory activity of the testicles had probably taken place. This lowered activity does not seem to have been caused by a damaging of the organ, which was histologically intact. It therefore seems inferable that the reduced function of the testicles depends on a decreased stimulation by gonadotropic hormone. The cause of this appears to be that the basophilic cells are engaged in the production of thyrotropic hormone and that the production of gonadotropic hormone suffers in consequence. In the females the cold-exposure reactions of the basophilic cells are weaker, and no lowering of the gonadotropic function has been detected in them.
Against this way of viewing the matter there might be a temptation to put up another interpretation. It might be assumed that it is the hormonic functions of the testicle that are reduced direct by the action of the cold. The consequence of this would be considered to be an atrophy of the accessory genital organs and a castration effect on the pituitary, with changes in the basophilic cell picture. This has not been the case for the following reasons. The only way by which cold can act direct on the testicles seems to be by giving rise to cellular injuries, and no such have been detected. The changes of the basophilic cells in the pituitary are bound up with the thyroid gland and not with the testicles, since an increase in the production of thyrotropic hormone occurs, which cannot be expected to be the case when castration cells arise. That it is not a question of castration cells is shown, finally, by the fact that their vacuolization can be prevented by administration of thyroxine, whereas vacuolization cannot be prevented by this means in the castration cells. As the above-mentioned interpretation of the reactions of the basophilic cells can be refuted, the conclusion would seem to be that the hypophyseal production of gonadotropic hormone is reduced in male rats as a result of the exposure to cold. In Chapter 6 it was possible to draw the conclusion that a connexion exists between the reactions of the anterior pituitary baso-philes during the cold exposure and changes in the production of thyrotropic hormone. As increased hormone production necessitates increased work in the cells, the question arises whether the reactions of the basophilic cells are an expression of an increased cell-work. In that chapter different reasons were assembled which, taken together, show that an essential part of the increased cellular work of the anterior lobe after the cold exposure probably takes place in the basophilic cells. Since to this may be added the fact that the same changes in the basophilic cells as follow cold exposure arise in other states when the organism raises demands for increased thyroid activity, the conclusion that thyrotropic hormone is produced by the basophilic cells of the anterior pituitary lobe seems to rest on an extremely solid basis of probability.

Cautious judgement is required in applying to the analysis of the thyrotropic functional state of the anterior lobe those possibilities which have been obtained of contributing to our knowledge by a cytological approach, and which have been employed in the present investigation into the influence thyroxine, sympathetic innervation, and stalk connexion have on the anterior pituitary production of thyrotropic hormone. It seems to be especially important to take into account the influence of damaging agents and especially of such denegerative changes in the gonads not hypophysally conditioned and as can give rise to castration cells.

SUMMARY.

The cold reactions of the thyroid gland can be fitted into a chain of physiological mechanisms, in which the cellular reactions of the anterior pituitary lobe enter as a link. The influence of stalk transection on these reactions is discussed and the conclusion is drawn that the operation reduces the power of the individual cells in question to react. Thyroxine has been found to have a retarding action on that work of the anterior lobe cells which is associated with the production of thyrotropic hormone, but it is not possible at present to decide whether this action is direct or indirect.

While the pituitary cell-work connected with thyrotropic hormone production is going on, basophilic cells are being used up and new ones are being formed, which is probably the cause of the diminution in the size of the anterior lobe. After cold exposure, therefore, the basophilic cells cannot take part to the same extent as normally in the production of gonadotropic hormone. In
male rats, the basophiles of which show more pronounced reactions to cold, a decrease in the gonadotropic hormone production seems to occur.

A connexion has been shown to exist between the reactions of the basophilic cells under cold conditions and the production of thyrotropic hormone. These reactions are probably a manifestation of the increased cell-work which must be considered to be necessary for an increased production of the hormone. To this it may be added that the basophilic cells react in the same way to the cold exposure as when, under other conditions, the organism make demands for increased thyroid function. On the strength of this the conclusion that thyrotropic hormone is produced by the basophilic cells in the anterior pituitary lobe seems to rest on an extremely solid ground of probability.