# Factors affecting The Islets of Langerhans

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Diabetes results from the fact that not enough insulin is available to tissues. This may be caused by an *absolute deficit* in insulin secretion, as when the islets are destroyed or the pancreas removed, or it may result from a greatly *increased requirement* for insulin such as might occur in the first phase of the administration of diabetogenic pituitary extracts. It is conceivable, too, that under some circumstances insulin might be inactivated before reaching the tissues, or that the utilization of insulin by the tissues might be interfered with in some way. Whatever the underlying factor or factors may be, if insulin injections alleviate the condition then we are forced to the conclusion that a *relative* deficiency of insulin must be the direct cause of the changes characteristic of the disease. If this is so, then it is of some interest to learn as much as possible about the insulin-secreting structures, the islets of Langerhans; and it is of some importance to discover how their activity is regulated; how this function may be stimulated or depressed; or by what means their cells may be damaged and destroyed. The means by which the islet cells may be destroyed comes more properly under the heading of experimental diabetes, so the discussion here will be confined largely to a consideration of the regulation of the activity and the growth of islet cells. This regulation becomes especially significant when we appreciate that much islet tissue is still present in many adult diabetics.[1]

The islets constitute about 1 per cent of the weight of the pancreas, and while we ordinarily think of them as fixed structures, they do actually exhibit a remarkable lability associated with the need for insulin. It should be pointed out that growth of the islets is one evidence of islet stimulation. As a rule, those factors causing islet growth are factors which would appear to cause secretion also. In young, growing animals, certain factors stimulate the islets to grow and secrete. In the sensitive adult dog, the same factors also stimulate growth, and secretion, but the stimulation may be excessive in relation to the growth, and the islets degenerate and the animal becomes diabetic. While stimulation of the islets is necessary for normal activity and growth, it must always be borne in mind that excessive stimulation may lead to exhaustion of the islet cells, degeneration of those cells and diabetes. Thus, stimulation of the islets under one set of circumstances leads to an increase in islet mass and an increased potentiality for insulin secretion, whereas under another set of circumstances strong stimulation of the islets may lead to their exhaustion and degeneration. The point to be made at this time is that growth of the islets is one evidence of islet stimulation.

## FACTORS INFLUENCING GROWTH

Many factors influence islet activity and growth, but for the most part these can be grouped as dietary and hormonal factors. Among the dietary factors the first one of importance is caloric intake.[2] If the intake of a balanced diet is so reduced that the individual fails to gain weight and the body weight remains constant, then the islets also fail to grow. If to the basal diet, equicaloric supplements of carbohydrate, protein or fat are added, then the animals receiving the carbohydrate or protein supplements show a significant increase in islet tissue, whereas the animals with the fat supplement do not.[3] Both carbohydrate and protein stimulate islet growth,[4] whereas fat does not. Similar conclusions concerning the effect of diet on islet activity have been derived from experiments concerning the insulin content of the pancreas and other studies.[5, 6] The conclusion from the diet work is that in order to have normal activity and growth of islets there must be a sufficiency of calories and a sufficiency of carbohydrate or protein (from which carbohydrate may be formed). If the caloric intake is

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reduced, or the carbohydrate intake is reduced, then islet activity and growth are depressed, whereas increasing the carbohydrate intake stimulates islet activity and growth. Excessive stimulation of the islets can be prevented by the reduction of caloric intake or restriction of carbohydrate supply.

Other evidence for a stimulating effect of carbohydrate is the finding that the continuous intravenous infusion of glucose occasions a greater than normal growth of the islets.[7, 8] This enhancement of islet growth is obtained despite the fact that, after six to 24 hours, the blood sugar level may be back within the normal range. While there is good evidence that an elevation in blood sugar level may stimulate the secretion of insulin, a marked elevation of blood sugar level does not seem to be the only stimulating factor. In these infusion experiments, the stimulation seems to be related to the total amount of carbohydrate administered in a given period rather than to any *large* change in blood sugar level.

## HORMONAL FACTORS

The hormonal factors influencing the islets are numerous. Insulin, the hormone produced by the islets, when given in large amounts depresses the growth of the islets and the production of insulin by their cells.[9] Indeed, experimentally, this depression of islet activity may under certain circumstances be great enough to produce a temporary diabetic state.

One endocrine gland whose functions seem in many, though not all, respects to be antagonistic to that of the *endocrine pancreas* is the anterior pituitary gland. When certain of its products are present in excess, more insulin is required or diabetic effects are observed. In sensitive adult dogs or in partially depancreatized animals of several species, including the rat, certain anterior pituitary extracts are diabetogenic.[10, 12] The diabetogenic effects can be prevented by giving insulin.[13, 14] In the intact rat the extracts do not produce diabetes, presumably because the islets themselves can sufficiently increase their insulin supply. The islet tissue in the rat is increased by daily injections of crude saline extracts of the anterior pituitary gland.[15, 16] Even in dogs in which these extracts are diabetogenic, signs of new formation of islet, acinar and duct cells are evident.[17] The increase in islet tissue in the rat, and signs of mitotic activity in the islets in the dog, have been taken as evidence of a pancreatropic effect. While it is true that pituitary extracts stimulate the islets, removal of the pituitary does not lead to atrophy of the islets.[18] Hence, a true tropic effect on the islets has not been established. However, the removal of the pituitary gland does prevent the islets from growing, but it also prevents the body as a whole from growing.

The crude pituitary extracts used to stimulate the islets contain a great variety of factors. The anterior pituitary gland influences the adrenals, thyroid and gonads through tropic principles, as well as peripheral tissues in general through the growth hormone. Figure 1 shows the effects of some highly purified pituitary principles on islet weights, and compares these with the effect of a crude saline extract of the anterior pituitary

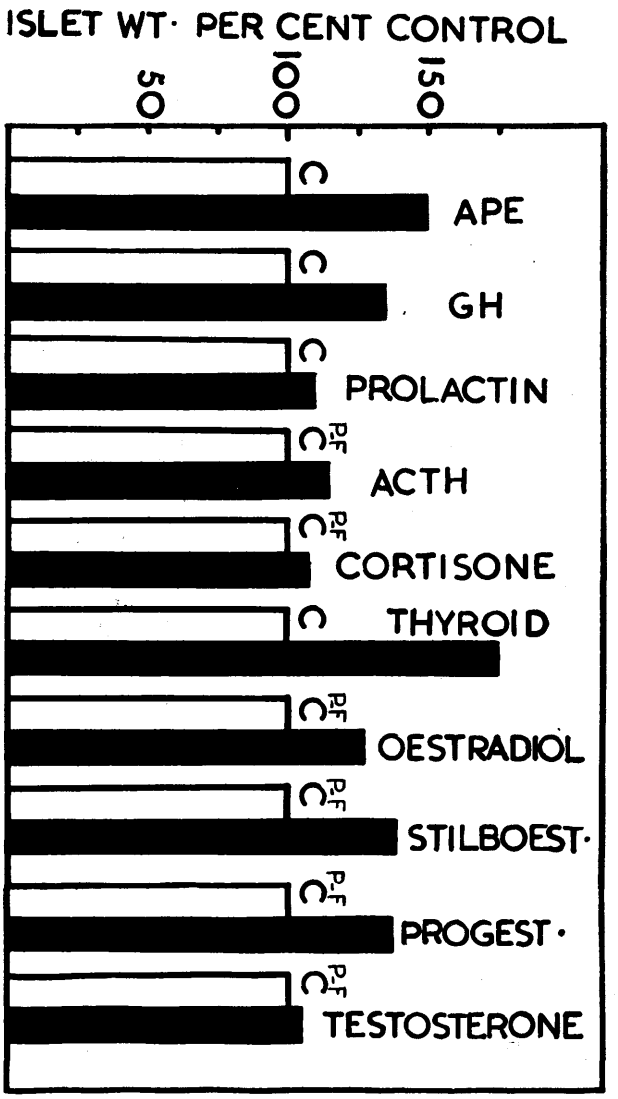


**FIGURE 1** The effects of some pituitary, adrenal, thyroid and gonadal substances on islet weights in intact rats.

Key: APE = anterior pituitary extract, GH = growth hormone preparations, ACTH = corticotropin. Stilboest. = diethyl stilboestrol, Progest. = progesterone. Islet weights in control animals are represented as 100.



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gland.[16, 19, 20] Where the pituitary tropic principles were not tried, the effects of certain hormones of their target organs have been tested. Thus thyrotropin was not tried, but the effect of the administration of desiccated thyroid gland was investigated.[21] Gonadotropins were not tested but the effects of certain sex hormones were studied[22].

To permit comparisons, the islet weights in the control animals for each experiment are shown as 100 in each instance and the test values scaled accordingly. Crude anterior pituitary extract (APE), growth hormone preparations, thyroid, estradiol benzoate, diethylstilboestrol and progesterone all caused significant increases in islet tissue. Corticotropin (ACTH) did too, but although the increase was significant it cannot be considered extensive.* The effects of prolactin, cortisone and testosterone were not significant in the intact animals.

To see if these effects were mediated through the pituitary gland, the pituitary was removed and certain of the materials were tested again.

All the substances shown in Figure 2 were effective in causing significant increases in islet tissue in hypophysectomized rats. Some of these caused the body weight in the hypophysectomized animals to increase; some of them had little effect on body weight; some caused the body weight to fall.

*The effect is greater if given by continuous intravenous infusion.

When the islet weight is expressed in relation to the body weight (Figure 3) then we see that in comparison with the influence on the body as a whole, cortisone, corticoptropin and thyroid administration have very profound effects on the islets. Of all the stimulating factors, thyroid seems to be particularly interesting and to have a good effect in intact and hypophysectomized rats,—an effect not related to a change in body weight.

The pituitary is not essential for the maintenance of the endocrine pancreas, for considerable periods of time at least, but the pituitary is necessary for the growth of the islets. It is also necessary for growth of the animal as a whole. Islet growth may be related to the growth of the animal as a whole and to the effect this has on insulin requirements, rather than to any specific effect of the pituitary apart from this. Other things which prevent body growth, such as the restriction of caloric intake, also prevent islet growth. However, with some materials islet growth is out of proportion to body growth and it may be that islet growth and body growth are quite independent. The information presented in this paper is summarized in Table 1.

## SUMMARY

The fact that several different substances seem capable of stimulating islet growth makes one feel that their effects are probably brought about through some final

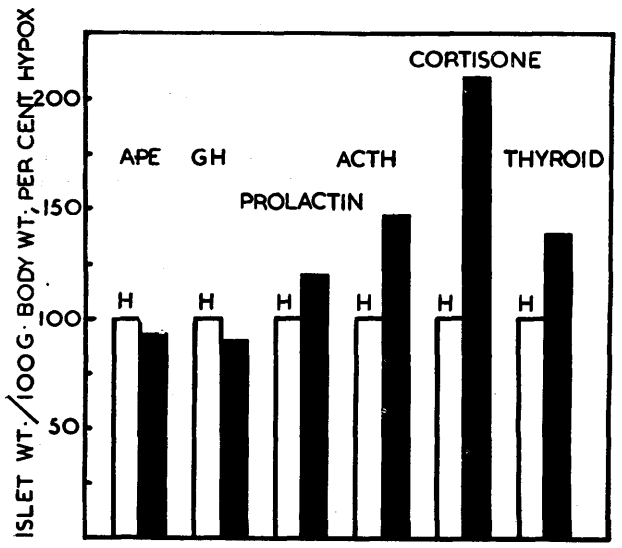


**FIGURE 2** The effects of some pituitary, adrenal and thyroid substances on islet weights in hypophysectomized rats.

Key: Hypox. = hypophysectomized, APE = anterior pituitary extract, GH = growth hormone, ACTH = corticotropin. Islet weights in control animals are represented as 100.

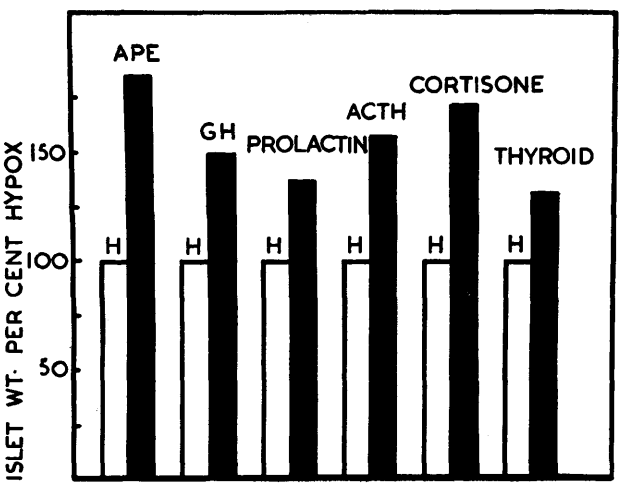


**FIGURE 3** The effects of some pituitary, adrenal and thyroid substances on the islet weights per 100 g. body weight in hypophysectomized rats.

Key: Hypox. = hypophysectomized rats, APE = anterior pituitary extract, GH = growth hormone, ACTH = corticotropin.



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**TABLE 1** Factors Reducing Islet Activity and in Young Rats Depressing Islet Growth

1. Restriction of caloric intake. Restriction of carbohydrate intake.
2. Administration of large amounts of insulin.
3. Removal of the pituitary gland.

Factors Stimulating Islet Activity and in Young Rats Increasing Islet Growth

| | Condition of Animal | |
|---|---|---|
| | Intact | Pituitary Removed |
| 1. High carbohydrate intake. | | |
| 2. Continuous injection of glucose. | | |
| 3. Injections of anterior pituitary extract: | + | + |
| 4. Injections of growth hormone preparations: | + | + |
| 5. Injections of corticotropin (ACTH) | +(slight) | + |
| 6. Injections of cortisone: | Not sig. | + |
| 7. Thyroid administration: | + | + |
| 8. Estradiol benzoate: | + | Not done |
| 9. Diethyl stilboestrol: | + | Not done |
| 11. Testosterone: | + | Not done |
| 10. Progesterone: | Not sig. | Not done |

common path. It seems altogether likely, from other work, that the materials which stimulate the growth of the islets do so because they increase the need for endogenous insulin, though the manner in which this requirement is transmitted to the pancreas is not known.

In conclusion, it should be pointed out again that excessive stimulation of the islets under some conditions can lead to degeneration and finally to disappearance of the insulin-secreting cells. It should also be emphasized that those factors reducing islet activity can prevent this excessive stimulation and protect the islets.

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