A Sequential Appraisal of Glucagon

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Glucagon, discovered and named thirty-three years ago,[1] has not yet been unqualifiedly accepted as a hormone. No clinical disorder attributable to deficiency or excess of glucagon has been established. This is perhaps not so serious because, for example, there could be no doubt of the hormonal nature of epinephrine but no syndrome referable to a deficiency of adrenal medullary secretion is known. Furthermore, evidence accumulates that glucagon secretion is increased by hypoglycemia, by insulin, by growth hormone and by adrenocorticotrophic hormone, and a "hyper" picture may be presented by the obesity hyperglycemia syndrome of mice.

It took a considerable time for us to revert to the Murlin name (glucagon), for the best early studies on the substance were those of Sutherland and Cori who called it the "hyperglycemic-glycogenolytic factor" (HGF). Its resemblance to, but difference from, epinephrine was soon established. Glucagon resembles epinephrine in that both stimulate glycogenolysis and both promote transformation of inactive to active phosphorylase. Glucagon differs from epinephrine in that glucagon has *no* effect on blood pressure, heart rate or eosinophile response, and the glucagon glycogenolytic effect is not blocked by adrenergic blocking agents which are capable of blocking epinephrine.[2] Furthermore, unlike epinephrine, glucagon does *not* produce a breakdown of muscle glycogen to lactate or pyruvate.

Chemical and Physico-chemical Properties of Glucagon. A considerable time ago, Sopp[3] showed that glucagon was a protein closely related to insulin. In 1953 and 1954 Staub and his associates[4] completely purified glucagon and began to characterize the molecule extensively. In 1955[5] he continued to characterize the pure substance. Its molecular weight is 4,200. Unlike insulin, it contains no cystine, proline, or isoleucine, but does possess methionine and tryptophane (absent in insulin), and can crystallize in the absence of zinc or other metals (crystalline glucagon has less than 0.01 per cent zinc). Furthermore, its amino-acid composition shows that it can *not* be a decomposition product of insulin.

Site of Origin. Immediately following the discovery of insulin, Macleod and Collip, encountering the brief but significant hyperglycemia, called this paradoxical. It was not found in Abel's crystalline insulin and therefore correctly attributed by Gerling to a contaminant, for which Murlin in 1924 suggested the name glucagon and the possibility that it was a physiologic substance.

Glucagon occurs in commercial insulin, in the perfusate and extracts of normal pancreas and the beta-cell-free pancreas of alloxanized animals and the duct ligated acinae-free pancreas. It is hence an islet cell product not produced by the beta cells and it seemed reasonable to assign its secretion to the alpha islet cells. Success in the chemical destruction of the alpha cells should have settled this but the employment of cobalt as an alpha-cytotoxic substance was unfortunate.

Volk, Lazarus and Goldner[6] showed that extracts of the pancreas of normal or alloxanized dogs, in which alpha cells have "almost entirely" disappeared after cobalt administration, still contain apparently normal quantities of a hyperglycemic principle. Fodden and Read[7] have shown that the pancreas from cobaltous chloride-treated rabbits contains an appreciable quantity of material with hyperglycemic activity, but that Synthalin A treatment leaves little hyperglycemic activity in the pancreas. A significant study of the glucagon content of pancreatic tissue devoid of alpha cells has now been made by Bencosme et al.[8] They showed that extracts of the uncinate process of the dog's pancreas, which contain no A cells, show virtually no hyperglycemic activity even when large aliquots of pancreas were used.

We are not yet clear as to whether extrapancreatic enterochromaffin cells secrete glucagon. Sutherland did not secure glucagon from the stomach of the hog where argentaffin cells are nevertheless present. According to Fodden,[9] these cells are *not* identical with pancreatic alpha cells. The two cells differ in response to several alphacytotoxic substances. It appears that stomach extracts may have an epinephrine-like substance with action like glucagon on liver slices. Finally, Ferner's claim that alpha

Presented at the Symposium on Insulin, Glucagon and the Oral Hypoglycemic Sulfonylureas sponsored by The Clinical Society of the New York Diabetes Association, Inc., on Oct. 12, 1956.

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cells hypertrophy with growth hormone and atrophy after hypophysectomy has received no confirmation. Islets and their cells are apparently seldom hypertrophied.

Relations of Glucagon to Insulin and the Anterior Hypophyseal Hormones. Let us next consider the relations of glucagon to insulin and the anterior hypophyseal hormones, as indicating a true physiologic role of glucagon in carbohydrate homeostasis. Pancreatectomized patients and animals need less insulin for regulation though they are less resistant to ketosis. Insulin sensitivity is greater in depancreatized dogs than in dogs treated with alloxan and the depancreatized dog becomes more ketotic than the alloxanized dog when insulin is withheld. The effect of pancreatectomy on insulin requirement is *not* due to faulty absorption of foodstuffs due to the lack of pancreatic enzymes, for in the alloxan diabetic dog ligation of the pancreatic ducts does not diminish the higher requirement for insulin.[10] The cross-circulation experiments of Foa et al.[11] suggest that the pancreas secretes glucagon in response to insulin-induced hypoglycemia. Sherlock,[12] in studying the response of the liver to insulin, has done hepatic vein catheterizations in man. When insulin was administered, hepatic glucose output was decreased at once; later there was more glucose and the blood sugar was restored to normal. An increase in glucose output precedes the increased hepatic blood flow and lactic acid output which occur when epinephrine is secreted. This may be due to glucagon secretion or as a direct hepatic response to hypoglycemia without need for glucagon intervention. Now, Laurence and Stacey[13] have shown that hexamethonium which is supposed to block sympathetic impulses to the adrenal medulla, does not delay the return of the blood glucose to normal after insulin-induced hypoglycemia. Hence, possibly glucagon is involved. It is interesting, in view of Foa's and of Sherlock's work, that MacGrath and Snedecor[14] have shown that in animals chronically treated with insulin the glucagon content of the pancreas is increased.

Growth hormone administration elicits the secretion of glucagon from the pancreas. Bornstein et al.[15] showed that blood from the pancreaticoduodenal vein of growth hormone-treated cats contains a blood sugar-raising substance which is *not* demonstrable in the femoral vein blood from the same animals. With his cross-circulation technic, Foa[16] has obtained similar findings. It seems exceedingly important that Fodden and Read[17] have been able to isolate a hyperglycemic phosphorylase-reactivating substance from canine pancreatic blood. They showed that a threefold increase in this hormone resulted from pretreatment with growth or adrenocorticotrophic hormone.

In Mayer's[18] studies genetically obese mice have increased glucagon in their pancreas and they respond with marked hyperglycemia to growth hormone administration, whereas nonobese litter mates show *no* such responses.

Van Itallie[19] has some remarks on the subject of an insulin *antagonist* (DeDuve, Ferner, etc.). The word antagonism is often too loosely used in biology. Because sympathetic and parasympathetic nerves may have "opposing" effects on smooth muscle, these systems are presently referred to as "mutually antagonistic." Actually, the nerves of these two systems act synergistically. The most generally agreed-to concept of the action of insulin is that it facilitates the entry of glucose into cells. There is evidence that growth hormone is antagonistic to insulin in this respect,[20] but the evidence with glucagon is conflicting. It most certainly appears that glucagon does *not* interfere with the action of insulin in promoting glucose transfer in peripheral cells. In the sense that glucagon raises the blood glucose whereas insulin lowers it, glucagon is an anti-insulin factor. By the same token, ingested carbohydrate would have to be called an anti-insulin substance, and this would reduce the concept of insulin antagonism to nonsense.

Finally, no conclusive evidence at present exists that glucagon has any primary physiologic action other than to stimulate hepatic glycogenolysis.[21] Its *physiologic* role has yet to be established. That there is an actual physiologic, sensitive interplay of output of glucagon and insulin has not yet been established in spite of an immense amount of work, for instance, that by Anderson,[22] who described fluctuations in the glucose content of hepatic venous blood as due to periodic glucagon releases. Pancreatectomized or cobalt or Synthalin-treated dogs must be used to establish this.

Etiology of Diabetes Mellitus. Is there as yet any bearing of our knowledge of glucagon upon concepts of the etiology of diabetes mellitus? It has certainly not been established that the disease diabetes, or that pancreatectomy diabetes or meta-hypophyseal diabetes result from an oversecretion of glucagon.

SUMMARIO IN INTERLINGUA

Estimation Currente del Studios de Glucagon

Es summarisate, super le base de referentias historic, le stato presente del investigation del natura, del origine, e del function del factor hyperglycemic glycogenolytic que es currentemente designate como glucagon.

Glucagon es un proteina relationate a insulina. Illo differe de insulina in certes de su amino-acidos in un tal

maniera que illo non pote esser considerate como un producto del decomposition de insulina.

Le question de qual cellulas pancreatic es le sito de origine de glucagon remane controverse, e il es non ancora clar si o non cellulas enterochromaffin extrapancreatic secerne glucagon.

Es listate varie studios relative al interdependentia functional de glucagon con insulina e hormon de crescentia. Es concludite que al tempore presente nulle primari action physiologic de glucagon es establite excepte su stimulation de glycogenolyse hepatic.

Quanto al rolo possibile de glucagon in le etiologia de diabete mellite, le facto es sublineate que il existe nulle prova que le morbo diabete o le diabete que resulta de pancreatectomia o diabete meta-hypophyseal es effectuate per hypersecretion de glucagon.

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