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HORMONAL FACTORS OF DIABETIC KETOSIS

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HORMONAL FACTORS OF DIABETIC KETOSIS

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SVMMARIVM — Diabetica canis chetosis causam habet in insulinae defectu et in hypophysariis et corticoadrenalinicis hormonibus simul exstantibus. Illustrat deinde Auctor hormonales factores in quibusdam simiis cynocephalis, in muribus, in hominibus.

Acetoacetic acid, acetone and D (-) β hydroxybutyric acid (which is not a ketone) are the so-called ketone bodies. They are found in small quantities in normal blood (ketonemia) and urine (ketonuria). When they are in abnormally large amounts the condition is called ketosis.

Ketone bodies are metabolic products of fatty acids originated in lipids and proteins. In ruminants the *fatty acids* are also absorbed directly from the digestive tract.

Ketone bodies increase when a sufficient amount of carbohydrate is not available, due to insufficient intake, as in fasting; to hypoglycemia; to uncompensated metabolic requirements; or to metabolic disturbances, as in uncontrolled diabetes mellitus and experimental diabetes. The last two of these conditions are the only ones considered in this lecture.

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(1) With collaboration of E. URGOITI, C. T. RIETTI, MARIA ELISA GALLI and E. DEL CASTILLO jr.

The syntheses of fats, carboydrates and protein diminish, or even cease, when there is complete or marked carbohydrate insufficiency. The decrease in available energy due to carbohydrate insufficiency provokes a compensatory increase in fat and protein catabolism. Proteins are converted partly into acetate and partly into glucose (gluconeogenesis). Lipids in stores are mobilized as non esterified fatty acids (NEFA) [6] which are carried by the blood to the liver where they are deposited and catabolized as ketone bodies.

In severe uncontrolled diabetes there is an increase in: *a*) the mobilization of free fatty acids in the fat stores; *b*) the amount of free fatty acids [6] and other lipids in the blood (hyperlipemia); *c*) deposition of lipids in the liver (fatty liver) and other tissues (kidney, muscle, etc.); *d*) catabolism of fatty acids in the liver, with abundant formation of ketone bodies which pass into the blood in excess of the amounts which the tissues can utilize, so that they accumulate in the body fluids and are eliminated in the urine.

The ketosis of diabetes appears to be primarily a result of overproduction of acetoacetate by the liver and, secondarily, to normal or under utilization of both acetoacetate and D (-) β hydroxybutyrate by the extrahepatic tissues, principally muscle [8] [29] [32].

The liver is the source of ketone bodies in diabetes, because of the rapid uptake and increased oxidation of fatty acids in the mitochondria [7] [17] [18], with excessive production of ketone bodies. The liver takes up non esterified fatty acids (NEFA) proportionally to their concentration in the blood. The plethora of fatty acid in the liver undergoing oxidative degradation in the mitochondria makes for an abundance of ketone bodies. The ketonemia of diabetic animals is well correlated to the lipid contest of their livers [29] with few exceptions [9] [35].

During the last 15 years great advances have been made in our knowledge of the metabolism of fatty acids and the

biochemistry of ketosis [4] [8] [16] [20] [21] [22] [36]. They will not be discussed here; only the principal hormonal factors involved in the production of diabetic ketosis will be considered.

HORMONAL FACTORS IN PANCREATIC DIABETES

The production of diabetic ketosis in pancreatectomized animals is due to the simultaneous action of two factors: 1) lack of insulin; 2) the presence of hypophyseal and adrenal hormones.

Insulin. — Diabetic ketosis occurs when there is a lack of insulin after pancreatectomy, or severe lesions in the β cells (alloxan diabetes), or the neutralization of insulin (anti-insulin serum). Insulin is the physiologic antiketogenic hormone; its action is rapid and intense, except when there are factors causing insulin resistance in the tissues.

The best known physiological action of the secretion of insulin is the regulation of the normal blood sugar level, the prevention or correction of the hyperglycemia.

Insulin has many metabolic actions: 1) it increases the uptake and utilization of glucose (muscle, fat) with the formation of glycogen, specially in severe diabetes; 2) it increases the formation of fatty acids in adipose tissue, decreases mobilization of fatty acids in depots, and prevents or corrects the accumulation of fat in the liver and Kidueys; 3) it prevents or corrects diabetic ketosis; 4) it is necessary for growth and for the action of somatotropin on protein synthesis and growth; 5) it presents or corrects the increase in protein catabolism observed in pancreatic diabetes.

In pancreatic diabetes the following metabolic disturbances are present:

1) hyperglycemia; diminished utilization of glucose; a decrease in glycogen, first in the liver and at later stages in muscle, but an increase in the heart, kidney, leucocytes, etc. in relation with the level of hyperglycemia;

2) increased mobilization of non esterified fatty acids (NEFA), marked hyperlipemia, fatty liver and kidney;

3) increased liver ketogenesis [32] with overflow of ketone bodies into the blood; increased ketonemia and ketonuria; acidosis. Between 50 and 75% of the ketone bodies is made up by D (−) β hydroxibutyric acid.

Insulin corrects all the metabolic disturbances of diabetes. This correction takes place very rapidly for the decrease in the uptake of glucose, hyperglycemia and ketosis; glycogen formation in muscle and liver increases rapidly. Other metabolic disturbances in the liver (lipogenesis, etc.) are corrected more slowly.

Diabetic ketosis is present in all types of diabetes if sufficiently severe: 1) diabetes mellitus; 2) diabetes following pancreatectomy; 3) diabetes caused by antiinsulin serum; 4) diabetes due to severe lesions in the β cells caused by toxic substances (alloxan, etc.); 5) diabetes provoked by hormones: diabetes hypophyseal, metahypophyseal, corticoid, metacorticoid, tyroid and metathyroid. Ketosis is also present in phlorizin glycosuria, which is accompanied by hypoglycemia.

The intensity of ketosis after pancreatectomy varies in different animal species: *a*) it is very high in the dog, cat, rat, man and baboon; *b*) mild in the rabbit, goat, pig, sheep and calf; *c*) it is not observed in the toad *Bufo arenarum* but it occurs with great intensity in the lizards *Tupinambis rufescens* and *T. texiguin*.

Role of hypophysectomy and adrenalectomy in pancreatic diabetes. — HOUSSAY and BIASOTTI found in 1929-1930 that extirpation of the pituitary (in the dog) [10] or its *pars distalis* alone (in the toad) [11] is followed by marked attenuation of pancreatic diabetes (dog, toad) and phloridzin diabetes (in the dog) [12]. In comparison with pancreatectomized animals the pancreatectomized-hypophysectomized dogs show: *a*) lower hyperglycemia and less glycosuria; in fasting animals hypoglycemia may develop, which can be fatal if not promptly treated

with glucose; 2) marked sensitiveness to insulin; 3) protein catabolism is less intense; loss of weight is less marked and survival is prolonged; 4) there is a slight or no increase in lipemia, no fatty liver or kidney and no increase (or only a slight increase) in ketonemia. These facts were observed in the dog [10], rat [29], baboon [9] and other species (including man). This remarkable lack of increase of ketonemia in hypophysectomized-pancreatectomized dogs was discovered by RIETTI [29] [30] who has made the determinations in the dogs studied by HOUSSAY and BIASOTTI [10]. The same lack of increase in ketonemia was observed after phloridzin administration by RIETTI [25] in the dog and AMATRUDA and ENGEL [1] [8] in the rat, etc.

Ketogenosis was found to be subnormal in liver slices of hypophysectomized rats [2] [34], and is increased by previous treatment by somatotropin. Ketogenesis is increased in liver slices of pancreatectomized-hypophysectomized cats, but is diminished to less than normal in those of pancreatectomized-hypophysectomized cats [3] [33]. Lipogenesis from acetate is minimal in liver slices of pancreatectomized cats, but the acetate is easily transformed into long chain fatty acids in liver slices of pancreatectomized-hypophysectomized cats [3] [33].

The action of the hypophysis in diabetes was discovered by HOUSSAY and BIASOTTI [10] [11], in 1930, by demonstration of the following facts: 1) severity of diabetes decreases following extirpation of the hypophysis (dogs and toads) or of its *pars* distalis (toad); and 2) implantation or injection of *pars distalis* re-establishes or even increases the intensity of pancreatic diabetes attenuated by hypophysectomy (in toads); 3) hypophysectomized animals are unable to maintain normal glycemic and glycogen levels during fasting.

LONG and LUKENS [19], in 1936, confirmed these observations and established the important fact that pancreatic diabetes is attenuated in a similar way by adrenalectomy. Ketosis, hyperlipemia and a fatty liver are not present in the adrenalec-

tomized-pancreatectomized animals [9] [19]. But the extirpation of only the adrenal medulla has no effect on the intensity of pancreatic diabetes [14] [26].

These facts were the first demonstration that: 1) the metabolic disturbances of pancreatic diabetes are due not only to lack of insulin but also to the presence of hypophyseal (and adrenocortical) hormones, which increase the severity of diabetes; 2) pituitary (and adrenocortical) hormones have a continous physiological action on carbohydrate metabolism in the normal and the diabetic states; 3) carbohydrate metabolism is regulated by a balance of hormones (pancreatic, hypophyseal, adrenal, etc.) which are in part antagonistic and in part synergic; 4) in diabetes, therefore, there is a disturbance in the balance of endocrine regulatory factors.

Ketogenic action of pituitary hormones

The diabetogenic action of pituitary extracts or hormones with increase of ketonemia, was demonstrated in dogs totally pancreatectomized, partially pancreatectomized, pancreatectomized-hypophysectomized, and in normal dogs [13] [26] [27].

The ketonemic action of pituitary extracts has been demonstrated by more than a hundred investigations after the first discovery by Burn and Ling (1930) [5]. This effect has also been obtained with somatotropin or adrenocorticotropin. Several specific ketogenic substances or hormones have been postulated but never isolated in a pure state, e. g. Fettstoffwechselhormon (Anselmino and Hoffmann, 1931), Orophysin (Magistris, etc.), etc.

Somatotropin [23] and adrenocorticotropin provoke mobilization of fatty acid from adipose tissue and increase lipemia. Other lipid mobilizers have been prepared from the pituitary gland and have been considered to be specific hormones [28] [30].

The ketonemic effect of hypophyseal injections has been observed in dogs after bilateral sympathectomy, removal of the adrenal medulla, castration [26] [27] and thyroidectomy [27].

Continuous intravenous infusion of somatotropin in man produces a biphasic effect: *a*) first a short lasting decrease (2 to 4 hours) of non esterified fatty acids (NEFA) and glycemia; *b*) later, there is a rapid increase of NEFA and a slow rise in glycemia.

This initial « insulinoid » hypoglycemic effect, followed later by resistance to insulin and a slow rise of the blood sugar to a hyperglycemic level, is more marked in certain conditions. An intense hypoglycemic response has been observed in adrenalectomized fasting rats, in hypophysectomized dogs, even when the pancreas had also been removed, and in other animals. Hypoglycemia of this type has caused the loss of many of our dogs which had been adrenalectomized-pancreatectomized, or adrenalectomized-hypophysectomized-pancreatectomized.

The two stages in the effect of somatotropin have also been demonstrated in the isolated rat diaphragm: 1) first there is a short lasting increase in the uptake of glucose and glycogen formation, and a decrease in the output of carbon dioxide; 2) later, the uptake of glucose diminishes and the action of insulin is also diminished.

Restoration of diabetic ketosis by hormones in pancreatectomized hypophysectomized or pancreatectomized adrenalectomized animals

Hypophysectomy, or adrenalectomy, produces attenuation or suppression of the hyperlipemia or hyperketonemia observed after pancreatectomy (Fig. 1). The separate action of somato-

Effect of Hypophysectomy and Adrenalectomy on Pancreatic Diabetes of Dogs and Cats (Average of Several Animals)

Animal	*Condition*	*Survival, days*	*Urine*			*G/N*	*Glycemia, mg. %*
			Glucose, gm. per kg. per day	*Nitrogen, gm. per kg. per day*	*Ketones, mg. per kg. per day*		
Dog....	Pancreatectomized.....	15	4.0	1.4	60	2.8	380
Dog....	Hypophysopancreatectomized..	74 (25–180) *	0.8 (0.05–3.2)	1.1 (0.4–2.1)	16 ...	0.8 (0.7–1.8)	234 (113–220)
Cat....	Pancreatectomized.....	5	3.2	1.3	116	2.7	347
Cat....	Hypophysopancreatectomized..	22	0.4	0.7	5	0.6	190
Cat....	Adrenalectomized-pancreatectomized	14	0.6	0.6	13	1.0	186

Source: Houssay and Biasotti (dogs); Long and Lukens (cats).

* Figures in parentheses are the extreme values.

FIG. 1 — Attenuation of diabetes and ketonuria of pancreatectomized animals by hypophysectomy (dogs) or adrenalectomy (cats).

tropin and of corticoids, or the association of both hormones has been studied in dogs, rats and baboons.

The experiments on dogs have been made by URGOITI, RIETTI and HOUSSAY, with the collaboration of M. E. GALLI and E. DEL CASTILLO jr. The animals were maintained in good conditions and were used without anesthesia. The groups studied were: *a*) normal dogs; *b*) pancreatectomized; *c*) pancreatectomized-hypophysectomized; *d*) pancreatectomized-adrenalectomized; *e*) pancreatectomized-hypophysectomized-adrenalectomized. During the experiments they did not receive insulin.

All the groups were studied: *a*) without treatment; *b*) during the three days when they were injected intraperitoneally with somatotropin (2 mg/kg, day); *c*) during three days when trated with cortisol acetate (2 mg/kg, day); *d*) during three days of simultaneous treatment with somatotropin and cortisol acetate.

In 26 normal dogs an average value of 2.4 $\pm$ 0.7 mg/100 ml of ketone bodies was found in the blood (Fig. 2).

In the pancreatectomized dogs, suppression of insulin was followed by a marked increase in ketonemia, which reached its highest level on the third day. The average in the course of 10 days was 27 $\pm$ 4 mg/100 ml of blood (Fig.2).

Insulin prevents or corrects partially or totally, according to the dose given, the diabetic disturbances: ketonemia, hyperlipemia and hyperglycemia of pancreatectomized dogs.

Other groups of pancreatectomized animals were maintained without insulin after hypophysectomy or adrenalectomy.

In the pancreatectomized-hyophysectomized dogs without insulin the following facts were observed:

a) the increase of ketonemia following the suppression of insulin was strikingly attenuated by previous hypophysectomy; it attained a maximal level of 4.0 $\pm$ 2 mg/100 ml of blood (average of 11 dogs) (Fig. 2);

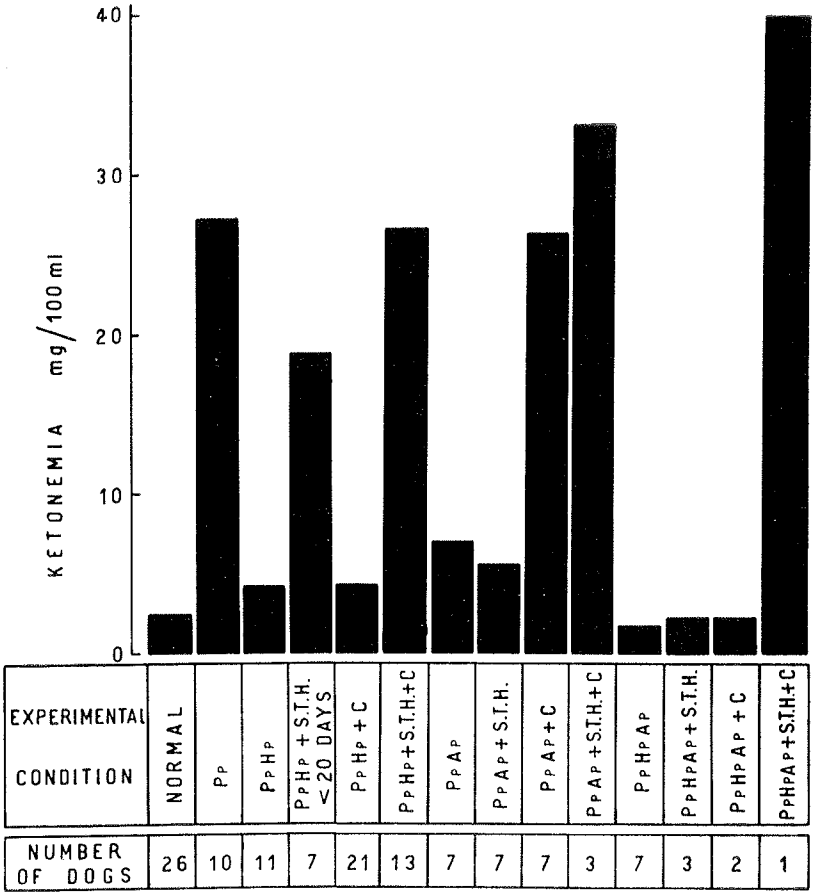

FIG. 2 — Ketonemia of dogs, normal, pancreatectomized (Pp). Pancreatectomized-hypophysectomized (Pp Hp), without treatment or treated by somatotropin (STH) or by cortisol (C) or both hormones. Pancreatectomized-adrenalectomized (Pp Ap), without treatment or treated by somatotropin (STH), cortisol (C) or both hormones. Pancreatectomized-hypophysectomized-adrenalectomized (Pp Hpr Ap), in the same conditions (URGOITI, HOUSSAY and RIETTI).

b) somatotropin administration increased the ketonemia of the pancreatectomized-hypophysectomized dogs, when injected 2 days after hypophysectomy, reaching the level observed in pancreatectomized dogs. Later, the ketogenic response to somatotropin diminished progressively during 20 days. The average ketonemic response during this period was 18.7 ± 7 mg/100 ml in 7 dogs. From the 30th to the 80th day after hypophysectomy the response was almost absent. The average of *10 dogs* during this period was 3.3 ± 2.7 mg/100 ml. (Fig. 3);

c) cortisol administration was not followed by significative increase of ketonemia which reached an average level of 3.8 ± 1.7 mg/100 ml on 21 dogs (Fig. 2);

d) associated administration of somatotropin plus cortisol determined a very intense increase in ketonemia, attaining the high level seen in pancreatectomized dogs after the suppression of insulin (Fig. 2).

In the depancreatized-adrenalectomized dogs without insulin the following facts were observed:

e) adrenalectomy strikingly attenuated the ketonemia of the pancreatectomized dogs deprived of insulin: 7 mg ± 1.5 mg/100 (average of 7 dogs) (Fig. 2);

f) somatotropin did not modify the ketonemia of these animals: 5.4 ± 3 mg/100 ml (average of 7 dogs); two dogs died with marked hypoglycemia a few hours after somatotropin injection (Fig. 2);

g) cortisol induced a sharp and intense hyperketonemia of 26.3 ± 5.5 mg/100 ml (average of 7 dogs) (Fig. 2);

h) the associated administration of somatotropin plus cortisol determined a very intense hyperketonemia of 33 ± 16 mg/100 ml (average of 3 dogs) (Fig. 2).

In the animals with the triple ablation: pancreatectomized-hyophysectomized-adrenalectomized, neither somatotropin nor

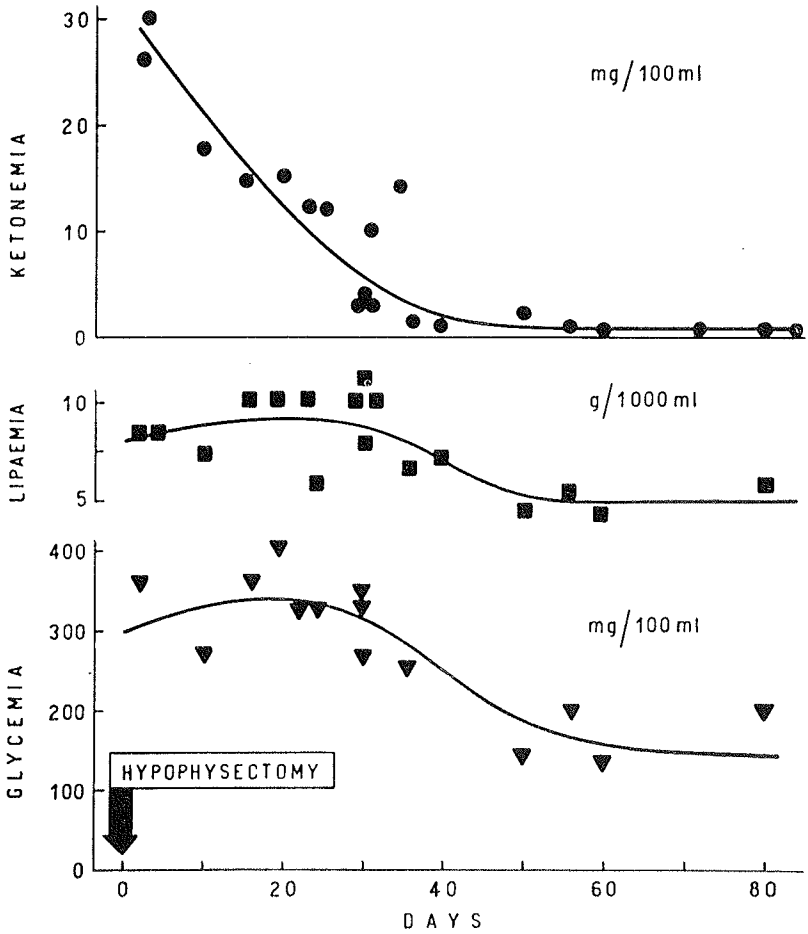

FIG. 3 — Ketonemia, lipaemia and glycemia of pancreatectomized-hypophysectomized dogs. Decrease of ketonemic action of somatotropin during the first 20 days after hypophysectomy and later on lack of ketonemic action.

cortisol increased the low level of ketonemia, but the association of both hormones produced an intense hyperketonemia in the only dog studied. Some dogs die in hypoglycemia when treated with somatotropin alone.

All these experiments demonstrated that *the production of diabetic ketosis in the pancreatectomized dog is dependent on two main groups of factors*: 1) *the first one is the lack of insulin;* 2) *the second one is the simultaneous presence of the pituitary and the adrenal glands (or their hormones). The presence of only one of these glands (or its hormones) is not sufficient; both of them must be present for the production of diabetic ketosis in the pancreatectomized dog.*

Insulin prevents or suppresses the increase of ketone bodies in pancreaterctomized dogs.

In the pancreatectomized dog the hyperketonemia is almost suppressed by hypophysectomy [11] [24] [25], and cortisol alone cannot re-establish it, due to the absence of the hypophysis.

In the pancreatectomized dog hyperketonemia is also markedly diminished by adrenalectomy [19] and somatotropin cannot re-establish it, due to the absence of the adrenal.

Cortisol restores the hyperketonemia of pancreatectomized-adrenalectomized dogs, because they have the hypophysis and the hormone replaces the adrenal. But cortisol has no ketonemic action in the pancreatectomized-hypophysectomized dogs, because they have no hypophysis.

The association of both hormones somatotropin and cortisol has an intense hyperketonemic action on all animals (pancreatectomized-hypophysectomized, pancreatectomized-adrenalectomized or pancreatectomized-hypophysectomized-adrenalectomized). The level of hyperketonemia obtained is similar to or higher than in the pancreatectomized dog.

The hyperketonemic action of somatotropin is observed in pancreatectomized-hypophysectomized dogs in full intensity two days after hypophysectomy. But the action of somato-

tropin diminishes from the second to the 20th day after hypophysectomy and later becomes vestigial or is absent (Fig. 3).

This change of response can be due to [1] a progressive diminution of secretion of corticoadrenal hormones; or [2] to a progressive decrease of some function of the tissues dependent on the adrenals caused by the diminution of corticoadrenal secretion, which falls to about 10% of the normal value a few hours after hypophysectomy. When corticoids and somatotropin are associated hyperketonemia rises to a high level. A similar phenomenon was found in liver slices of rats [34].

In most cases the hyperlipemia develops before the hyperketonemia in the experimental dogs. But there are a few important exceptions to this rule: 1) in pancreatectomized-hypophysectomized dogs the hyperketonemic action of somatotropin diminishes with time even though hyperlipemia is present (Fig. 4); 2) more striking is the fact that in pancreatectomized-hypophysectomized dogs treated with cortisol there is no increase of ketonemia in spite of the marked hyperlipemia (Fig. 4). In the pancreatectomized-hypophysectomized baboon similar facts have been also observed (Fig. 6 and 7): cortisone produces a severe lipemia but not an increase in ketonemia [9]. On the other hand, in the pancreatectomized-hypophysectomized baboon the injection of anterior lobe of human hypophysis does not raise the low level of serum lipids but rapidly causes a severe ketonemia [9] (Fig. 6).

In another group of dogs studied by RIETTI, URGOITI, GALLI and DEL CASTILLO the blood non esterified fatty acids (NEFA) are diminished by hypophysectomy, and strongly increased by pancreatectomy. The insulin corrects ketonemia of pancreatectomized dogs in spite that NEFA are still at a high level. In pancreatectomized dogs, the consecutive hypophysectomy prevents the increase of NEFA and ketonemia. In the same hypophysectomized-pancreatectomized dogs, somatotropin increases NEFA and ketonemia during the first 20 days after hypophysectomy; but after 30 days NEFA is increased

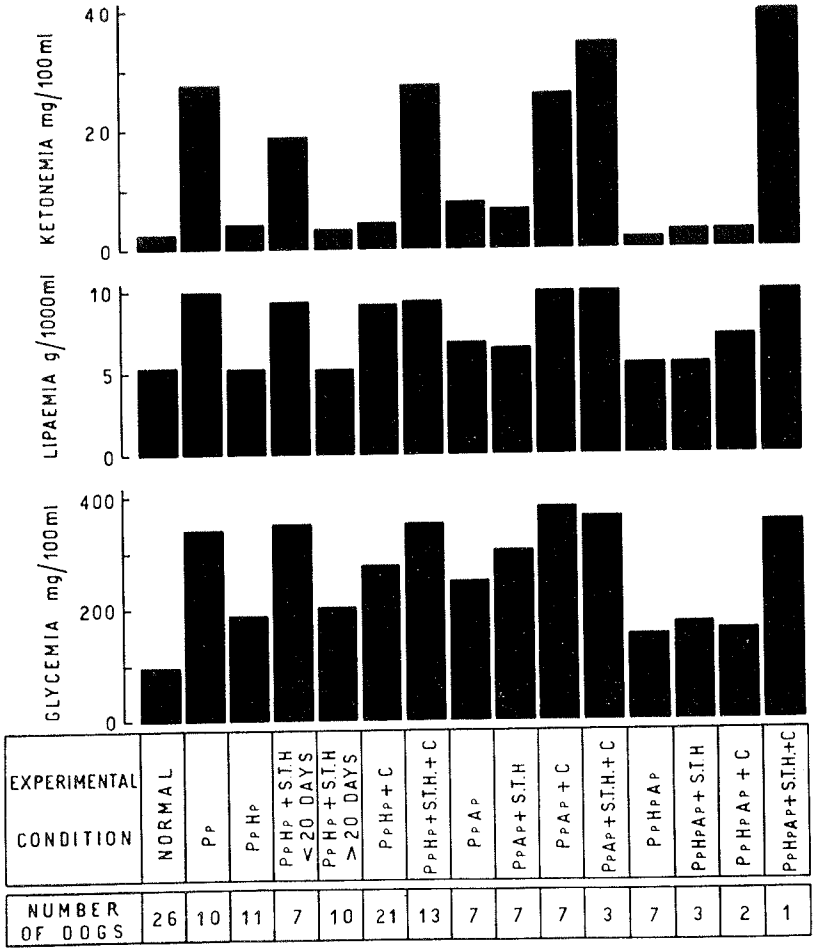

FIG. 4 — Dogs normal, pancreatectomized (Pp), pancreatectomized-hypophysectomized (Pp Hp), pancreatectomized-adrenalectomized (Pp Ap), pancreatectomized-hypophysectomized-adrenalectomized (Pp Hp Ap), treated by somatotropin (STH), cortisol (C) or both hormones (STH + C). Ketonemia, lipaemia, glycemia.

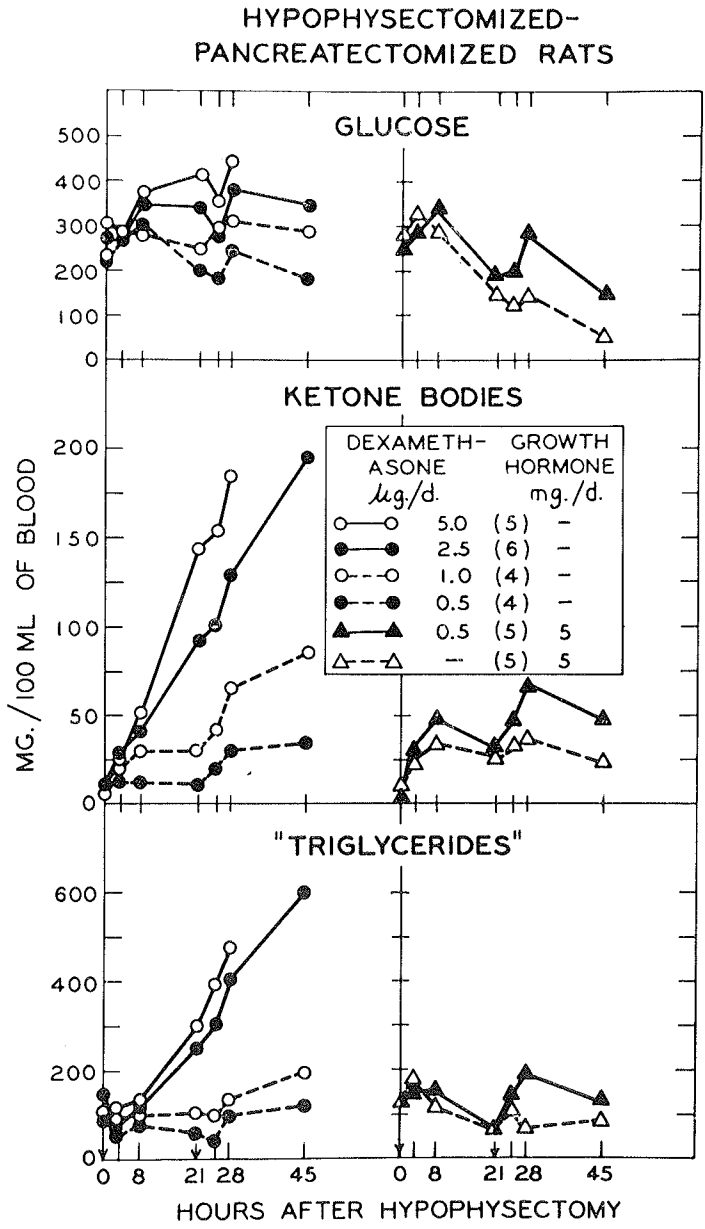

FIG. 5 — In hypophysectomized-pancreatectomized rat somatotropin has no ketonemic or diabetogenic action, cortisone produces both effects (SCOW and CHERNICK).

METABOLIC RESPONSES TO SOMATOTROPIN (STH), HUMAN ANTERIOR PITUITARY (HAL) AND CORTICOIDS (C) IN DOG, RAT AND BABOON

EXPERIMENTAL CONDITION	HYPERLIPEMIA			HYPERKETONEMIA		
	DOG	RAT	BABOON	DOG	RAT	BABOON
P_p	+++	+++	+++	+++	+++	+++
P_p-H_p	—	—	or mild	—	—	—
P_p-H_p+STH	+++ (1)	—		+++ (1)	—	
P_p-H_p+HAL			—	—	—	+++
P_p-H_p+C	+++	+++	+++	—	++++	—
P_p-H_p+STH+C	+++		+++	+++	+++	+++
P_p-A_p	—	—	—	—	—	—
P_p-A_p+STH	—	—		—	—	
P_p-A_p+HAL			—			Variable
P_p-A_p+C	+++	+++	+++	+++	+++	— (2)
P_p-A_p+STH+C	+++			+++		
P_p-A_p+HAL+C			+++			+++

P_p: Pancreatectomized_ H_p: Hypophysectomized_ A_p: Adrenalectomized
(1) When STH was injected from 2nd to 20th day after hypophysectomy_ (2) one case +

FIG. 6 — Lipaemia and ketonemia increases by action of pituitary hormones or corticoids, in animals; pancreatectomized (Pp), pancreatectomized-hypophysectomized (Pp Hp), pancreatectomized-adrenalectomized (Pp Ap).

moderately and ketonemia practically not. In the same animals administration of cortisol increases NEFA but practically not the ketonemia. The association of somatotropin and cortisol increases markedly NEFA and ketonemia.

The role of endocrine glands (and their hormones) differs in different animal species. The Dog, the Rat, the Baboon and Man can be considered comparatively. In all these species extirpation of the pituitary or adrenal prevents or strikingly reduces the hyperketonemia observed after pancreatectomy.

The role of the pituitary and the adrenal (or their hormones) in the diabetic ketosis of pancreatectomized rats has been masterly studied by R. O. Scow, who began this study in our Institute and continued it in the N. I. H. laboratories in Bethesda [29]. He was the first to have studied completely pancreatectomized rats maintained in good conditions.

INCREASE IN KETONEMIA IN PANCREATECTOMIZED-HYPOPHYSECTOMIZED INDUCED BY

	CORTICOIDS	S.T.H	CORTICOIDS + H.A.L	CORTICOIDS + S.T.H
DOG	—	+(2)		++
RAT	+	—		++
BABOON	—	+	++	
MAN	+(1)			++

(1) In 5, not in 1
(2) The first 20 days

FIG. 7 — Comparison of action of corticoids, pituitary hormones or association of both in pancreatectomized-hypophysectomized animals (dog, rat, baboon and man).

In the pancreatectomized-hypophysectomized rat somatotropin does not increase ketonemia (Fig. 5), as occurs in the Dog and the Baboon (Figg. 2, 6 and 7). Inversely in the pancreatectomized-hypophysectomized rat corticoids produce hyperketonemia, but not in the Dog or in the Baboon.

It is a well known fact that repeated injections of somatotropin can produce diabetes in normal dogs, but they do not produce the hyperglycemia or diabetes in the normal or pancreatectomized-hipophysectomized rat [19] [29] (Figs. 5, 6 and 7).

Cortisol is specially active on lipemia, because in the absolute or relative absence of insulin it produces hyperlipemia in dogs without hypophysis (hypophysectomized-pancreatectomized) or without adrenals (adrenalectomized-pancreatectomized and a slight hyperlipemia in pancreatectomized dogs deprived of both the adrenals and the hypophysis (Fig. 4).

The pituitary plays an important part in the increase of ketonemia in the dog and in the baboon when insulin is lacking. In these animals pancreatectomy is not followed by ketonemia in the absence of the pituitary or of somatotropin (Fig. 6).

GILLMAN suggests that in the Baboon the development of a severe hyperlipemia is dependent on an absolute or relative insufficiency of insulin coupled with an active secretion of ketogenic hormone from the pituitary, probably somatotropin, and the availability of an 11-oxycorticoid hormone. The latter is not required to be in excess of the amount of hormone produced by the adrenal cortex of the baboon following hypophysectomy. Severe ketonemia when there is not much insulin may depend on the presence of a factor in the adrenal cortex which releases the ketogenic component of the anterior pituitary.

In diabetic man, total hypophysectomy, or intense pituitary insufficiency, diminishes the requirement of insulin and provokes insulin sensitivity. But in clinical cases it is frequently difficult to establish how much insulin is still being produced by the pancreas and how complete is the hypophysectomy. The patients must be maintained by corticoids and thyroid hormones. The facts best established in these cases are: 1) ketosis can be controlled by a certain amount of insulin administration; 2) corticoids have a ketogenic action as in the rat; 3) growth hormone is ketogenic as in dogs, specially if the pituitary has

been exstirpated (Fig. 7). These cases of hypophysectomized juvenile diabetes received daily cortisone.

The action of other endocrine factors (thyroid, gonadal hormones, adrenalin, glucagon) is important in some aspects of fat metabolism and ketosis. In this lecture, we will not discuss them, nor the role of the sympathetic nervous system, because in their absence diabetic ketosis occurs after pancreatectomy.

We will not discuss here the ketosis of fasting or the ketosis of ruminants. The only points discussed in this lecture are the hormonal factors of diabetic ketosis of pancreatectomized animals, which is due at the same time to two factors: 1) the absolute or relative absence of insulin, which is of fundamental importance and 2) the simultaneous presence of the pituitary and adrenal glands (or their hormones) in absence or deficiency of insulin.

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