ENDOCRINE CONTROL OF BLOOD SUGAR, LIPAEMIA, AND KETONAEMIA IN DIABETIC BABOONS

BY

JOSEPH GILLMAN, D.Sc., M.B., CHRISTINE GILBERT, D.Sc., EDWARD EPSTEIN, M.B., B.Ch.

Departments of Physiology and Anatomy and Joint Nutrition Research Unit of the C.S.I.R. and of the University of the Witwatersrand, Johannesburg

AND

J. C. ALLAN, Ch.M., F.R.C.S.Ed.

Department of Surgery, University of the Witwatersrand

Complete removal of the pancreas from normal baboons, as in other mammals, leads to the development of the classical features of diabetes, including hyperglycaemia, ketonaemia and ketonuria, polydipsia, and polyuria. Investigation of the diabetic state in experimental baboons revealed that the severity of the ketosis could not be correlated with the degree of hyperlipaemia or with the hyperglycaemia, and that the extent of the hyperglycaemia did not influence the hyperlipaemia (Gillman *et al.*, 1958a). On the basis of experiments conducted in dogs, cats, and rats, it is generally believed that the fundamental disorder of carbohydrate metabolism in diabetic animals is alleviated by hypophysectomy, or by adrenalectomy, and that the administration of pituitary extracts and of adrenocortical hormones will once again restore the diabetic picture in depancreatized-hypophysectomized and in depancreatized-adrenalectomized animals respectively (Houssay and Biasotti, 1931; and Long and Lukens, 1936).

Reinvestigation of the role of the hypophysis and of the adrenal in depancreatized baboons not receiving insulin will show that the severity of the diabetes, as assessed by the hyperglycaemia and glycosuria, is not immediately alleviated by hypophysectomy although the clinical condition of the baboon is improved. It will also become apparent from the data presented below, taken in conjunction with previously reported experiments (Gillman *et al.*, 1958a), that each aspect of the disorder of lipid metabolism is dependent upon a particular pattern of endocrine function. It is suggested that analysis of the various lipid fractions in the blood as well as of the blood sugar and blood ketones in each human diabetic may afford a useful guide to the relative participation of the endocrine glands in maintaining the disorder of metabolism.

Material and Methods

Five male baboons were totally pancreatectomized, the entire gland being carefully dissected away from its intimate attachment to the duodenum. Between 2 and 14 months after pancreatectomy the baboons were totally hypophysectomized, a transorbital approach devised by one of us (E. E.) being employed for this procedure (Gillman and Gilbert, 1956). As the pituitary gland was removed under direct vision we were satisfied that no fragments remained. Moreover, when the baboons eventually came to necropsy, macroscopic as well as microscopical examination of the contents of the sella turcica revealed no sign of residual pituitary gland.

Three of the five depancreatized-hypophysectomized (D.-H.) baboons were subjected to various forms of endocrine therapy. Cortisone was administered on a body-weight basis—namely, 1 mg./kg. body weight—while thyroxine was given intramuscularly in amounts of 0.2 mg. three times a week. Acetone-dried anterior lobe of human pituitary gland, obtained from necropsy cases, was pulverized and

administered to the baboons as a suspension in normal saline by subcutaneous injection. At the time of each administration of crude pituitary the baboons also received 150,000 units of "seclomycin" as a prophylactic measure.

The daily insulin requirements of the D.-H. baboon ranged from 6 to 10 units in baboons weighing from 11 to 18 kg. The baboons received food *ad libitum* and maintained a steady body weight.

In all instances, blood samples for the estimation of the various lipid fractions, ketone bodies, and glucose were obtained at 9 o'clock in the morning, 16 hours after the last dose of insulin and the last meal. The total lipids were estimated by the nephelometric method of Kunkel *et al.* (1948), the total cholesterol according to the procedure described by van Zyl and Kerrich (1955), the lipid phosphorus by the method of Whitehorn (1924), with van Zyl's modification, and the ketone bodies according to the method of Werk *et al.* (1955).

Reactions in Depancreatized Baboons

After removal of the pancreas the suspension of insulin treatment for four days led in 15 baboons to a hyperglycaemia exceeding 400 mg./100 ml. and glycosuria, a threefold to sevenfold increase in total lipids (903–2,184 mg./100 ml.), a twofold to fivefold increase in total cholesterol (175–780 mg./100 ml.), a one-and-a-half to threefold increase in lipid phosphorus (12–34.6 mg./100 ml.), and a 4 to 47-fold increase in ketone bodies in the plasma (Gillman *et al.*, 1958a). Institution of insulin treatment restored the blood sugar, the blood lipids, and the ketone bodies to within normal ranges (Gillman *et al.*, 1958a, 1958b). Thus removal of the pancreas from baboons produces biochemical changes in the blood similar to those described in human diabetes.

Effect of Hypophysectomy in Depancreatized Baboons

Total hypophysectomy was carried out in five depancreatized baboons. Soon after operation it was noted that the glycosuria of the D.-H. baboons was not abolished and could be controlled only by the administration of insulin. However, the sensitivity of the D.H. baboons to insulin was greatly increased and the daily requirements were reduced to one-third or even one-fifth of the prehypophysectomy dose.

Two to four weeks after removal of the hypophysis the depancreatized baboons were subjected to a four-day period of insulin deprivation. With one exception the resting blood sugar rose within four days to levels exceeding those observed in the same baboons deprived of insulin prior to hypophysectomy (B. 384, Table I). In one D.-H. baboon deprived of insulin for 10 days the resting blood sugar of 750 mg./100 ml. increased to 1,332 mg. after a feed, a phenomenon which is attributable in part to the reduced efficiency of the kidney.

The most striking feature of the serum lipids in the D.-H. insulin-deprived baboons was the failure of the total lipids to reach levels comparable to those observed during insulin deprivation prior to hypophysectomy, even when insulin was withdrawn for as long as 10 days. The total cholesterol and lipid phosphorus showed a significant rise, and, with

the exception of B. 375 and B. 386, the values were comparable to those observed during insulin deprivation prior to hypophysectomy. Without exception the blood ketone bodies remained low, the maximum reading not exceeding 3.6 mg./100 ml. in B. 386 as compared with a prehypophysectomy level of 70 mg./100 ml. in the same baboon (Table I).

As in the case of the depancreatized baboons, the administration of insulin to D.-H. baboons following a period of insulin withdrawal was attended by a decrease in all the lipid fractions. Thus, removal of the hypophysis from depancreatized baboons did not alleviate the disorder of carbohydrate metabolism, but it prevented the severe ketosis and the severe lipaemia, affecting mainly the triglycerides.

Effect of Cortisone, Thyroxine, and Crude Anterior Pituitary in D.-H. Baboons

Unfortunately, B. 366 and B. 375 died before our experiments were completed. We are therefore only able to report on the effects of cortisone, thyroxine, and/or crude anterior pituitary on B. 384, B. 368, and B.386.

B. 384 (Table II, Experiments 1 to 3)

After hypophysectomy B. 384 was subjected to one experimental procedure involving the use of crude anterior pituitary. During a four-day period of insulin deprivation the baboon received a total of 0.29 g. of crude anterior pituitary administered in equally divided doses over the four days. The most noteworthy features were: (1) the severe ketosis, the level of the blood ketone bodies being twice as great as in the insulin-deprived baboon before hypophysectomy; and (2) the very high level of the resting blood sugar (1,100 mg./100 ml., experiment 3). The total lipids, cholesterol, and lipid phosphorus rose to levels higher than those observed in the same baboon deprived of insulin and not receiving crude pituitary (cf. experiments 2 and 3), although the lipaemia was not as severe as that observed in the same baboon when deprived of insulin before hypophysectomy (cf. experiments 1 and 3). The baboon became gravely ill, showing extreme polydipsia and abdominal distension. Despite the administration of four times the amount of insulin that was adequate in ordinary circum-

stances to prevent the baboon from passing into hypoglycaemic coma, the ketosis and the hyperglycaemia persisted for 24 hours after the last injection of crude pituitary. Death could not be prevented.

The administration of crude anterior pituitary to the D.-H. baboon deprived of insulin thus failed to restore the lipaemia to the prehypophysectomy level, but resulted in a ketosis and hyperglycaemia even more severe than that observed before hypophysectomy.

B. 368 (Table II, Experiments 4 to 9)

The daily administration of cortisone for a period of three weeks to the D.-H. baboon, B. 368, doubled the daily amount of insulin required to control the diabetes but did not affect significantly the level of the blood lipids. Withdrawal of insulin for four days was followed by severe hyperglycaemia and glycosuria and a lipaemia even more severe than that observed in the same baboon during insulin deprivation prior to hypophysectomy (cf. experiments 6 and 4). The ketone bodies in the blood remained low (2.8 mg./100 ml.) despite the intense lipaemia (cf. experiments 6 and 5). The institution of insulin therapy promptly reduced all the lipid fractions.

Pretreatment with cortisone and insulin for eight weeks was followed by a two-weeks course of thyroxine in conjunction with cortisone and insulin. Thereafter, withdrawal of insulin for four days precipitated an intense hyperglycaemia, glycosuria, and lipaemia, the greatest increase occurring in the cholesterol and total lipids, which reached levels higher than those in the depancreatized baboon deprived of insulin and having an intact pituitary (cf. experiments 7 and 4). Attention is drawn to the slight elevation of the ketone bodies (9.8 mg./100 ml.), which nevertheless remained low compared with the depancreatized baboon (75.2 mg./100 ml.). After the administration of insulin, the blood lipids returned to normal. Thereafter, the daily amounts of cortisone and thyroxine were gradually reduced and eventually completely withdrawn.

Apart from insulin, B. 368 received no hormonal treatment for six weeks. Insulin was then withdrawn for four days. During this period the baboon received a daily injection of 0.144 g. of crude anterior pituitary. On the third day the

TABLE I.—*Lipids, Ketone Bodies, and Glucose in the Blood of Male Baboons Before and After Pancreatectomy and Hypophysectomy*

Baboon No.	Before Pancreatectomy					After Pancreatectomy*					After Pancreatectomy-hypophysectomy*				
	Total Lipids	Total Cholesterol	Lipid Phosphorus	Ketone Bodies	R.B.S.	Total Lipids	Total Cholesterol	Lipid Phosphorus	Ketone Bodies	R.B.S.	Total Lipids	Total Cholesterol	Lipid Phosphorus	Ketone Bodies	R.B.S.
	mg./100 ml.					mg./100 ml.					mg./100 ml.				
366	420	144	10.0	—	73	1,370	225	12.2	—	410	567	185	13.5	2.7	640
368	384	122	8.5	—	83	1,274	234	17.4	75.2	424	565	236	12.0	2.2	562
375	441	129	11.3	—	93	1,369	294	25.0	12.0	550	548	186	10.5	2.0	666
386	401	126	9.0	—	70	2,113	540	15.8	70.4	430	537	203	12.5	3.6	540
384	332	124	8.5	1.8	87	948	175	12.0	15.4	601	395	152	9.0	3.0	392

* Estimations performed after a four-day period of insulin withdrawal.

TABLE II.—*Lipids, Ketone Bodies, and Glucose in Blood of Pancreatectomized-hypophysectomized Baboons Receiving Cortisone, Thyroxine, and Crude Anterior Pituitary at End of Four-day Period of Insulin Withdrawal*

Expt. No.	Baboon No.	Operation	Treatment	Total Lipids	Total Cholesterol	Lipid Phosphorus	Ketone Bodies	R.B.S.
				mg./100 ml.				
1	384	Pancreatectomy	Nil Crude pituitary	948	175	12.0	15.4	601
2		Pan. + hypophysectomy		395	152	9.0	3.0	392
3		"		594	216	14.0	33.0	1,100
4	368	Pancreatectomy	Nil Cortisone Cortisone + thyroxine Crude pituitary Cortisone + thyroxine + crude pituitary	1,274	234	17.4	75.2	424
5		Pan. + hypophysectomy		565	236	12.0	2.2	562
6		"		1,588	340	20.1	2.8	601
7		"		2,003	544	27.6	9.8	666
8		"		610	144	8.1	68.0	1,332
9		"		2,115	406	20.1	86.0	380
10	386	Pancreatectomy	Nil Thyroxine Cortisone + crude pituitary	2,113	540	15.8	70.4	430
11		Pan. + hypophysectomy		537	203	12.5	3.6	340
12		"		437	126	5.9	1.6	510
13		"		3,910	630	25.4	88.0	395

baboon became listless and anorexic. The outstanding feature of the blood chemistry in B. 368, as in B. 384, was the severe ketonaemia which approximated to that observed in the depancreatized insulin-deprived baboon (cf. experiments 8 and 4) and the profound hyperglycaemia, the blood sugar rising to 1,332 mg./100 ml. The total lipids were slightly elevated but much lower than in the D.-H. baboon receiving cortisone or cortisone and thyroxine but no insulin (cf. experiment 8, with experiments 7 and 6). By contrast, the cholesterol and the lipid phosphorus values were much reduced compared with those of the D.-H. baboon not receiving insulin (cf. experiments 8 and 5).

At the end of the four-day insulin-withdrawal period, B. 368, like B. 384, was found to be resistant to insulin and withstood the injection intravenously of 12 units of unmodified insulin and of 18 units of isophane insulin subcutaneously without developing signs of hypoglycaemia. Within 24 hours the blood sugar of B. 368 was reduced to 540 mg./100 ml. The low physical state of the baboon as well as the continuing poor appetite prompted us to begin cortisone treatment, at first intravenously (10 mg./day for six days) and thereafter subcutaneously (10 mg./day). Although the "toxic" effects of crude pituitary gland were to some extent counteracted by cortisone, as apparently occurs in dogs (de Bodo and Altszuler, 1955), a second baboon (B. 386) failed to respond to cortisone under similar experimental conditions.

After seven weeks of cortisone and insulin therapy, B. 368 received a three-weeks course of thyroxine in conjunction with cortisone and insulin. During this regimen the total lipids, cholesterol, and lipid phosphorus remained within the range recorded for the D.-H. baboon receiving insulin only. Insulin was then withdrawn for four days, and simultaneously a total of 0.508 g. of crude pituitary was given subcutaneously in equally divided doses over the first three days of insulin withdrawal. Again the baboon became severely ill. From experiment 9 it is evident that the biochemical findings in the blood, with the exception of the blood sugar, represent an exaggeration of the results obtained in the same baboon prior to hypophysectomy (cf. experiments 9 and 4). It is evident that in the D.-H. baboon, B. 368, the complete picture of diabetes, including severe hyperglycaemia, hyperlipaemia, and ketosis, could be reproduced by the administration of cortisone as well as crude pituitary, but by neither alone.

Recovery was facilitated by the administration of cortisone and thyroxine continued for a period of five weeks. Thereafter, both cortisone and thyroxine were withdrawn. During the succeeding five weeks, although small amounts of insulin were given daily, morning hyperglycaemia and glycosuria persisted. However, owing to the increasing sensitivity of the baboon to insulin even during the day, the administration of insulin was discontinued for four weeks. During this period the resting blood sugar, which had fluctuated hitherto from 250 to 400 mg./100 ml., suddenly decreased to hypoglycaemic levels (13 mg./100 ml.), thereby precipitating coma in the D.-H. baboon. Following an intragastric feed the blood sugar rose again to hyperglycaemic levels (400 mg./100 ml.), and was maintained at a high level as long as the animal consumed a minimum amount of food daily. It should be mentioned that after the episode of hypoglycaemic coma the baboon refused all food and had to be force-fed by intragastric intubation.

It is thus apparent that in the absence of insulin a depancreatized baboon may develop acute hypoglycaemia after removal of the hypophysis, especially following the suspension of a prolonged course of treatment with cortisone, which may have depressed still further an already underactive adrenal gland. Furthermore, this experiment indicates that (1) in the circumstances mentioned the D.-H. baboon failed to maintain a hyperglycaemia during short periods of starvation, and (2) the underlying defect in carbohydrate metabolism produced by removal of the pancreas was not alleviated by hypophysectomy.

B. 386 (Table II, Experiments 10 to 13)

Having shown that it was possible to reproduce the full diabetic picture in a D.-H. baboon by means of thyroxine, cortisone, and crude anterior pituitary, it became necessary to assess the role of the thyroid in this mechanism. The results of the experiments conducted in B. 386 are shown in Table II.

Prior to hypophysectomy B. 386 received a three-weeks course of thyroxine in conjunction with insulin. The total lipids, cholesterol, and lipid phosphorus remained unaltered. Withdrawal of insulin was attended by a marked rise in all the serum lipids, particularly in the lipid phosphorus, which increased by twofold in comparison with the insulin-deprived baboon not receiving thyroxine.

After hypophysectomy B. 386 again received a three-weeks course of thyroxine with insulin, followed by insulin deprivation for four days. During the withdrawal period the total lipids, the cholesterol, and the lipid phosphorus failed to rise (experiment 12). Thyroxine thus prevented the increase in the serum lipids which had been consistently observed, to a greater or less extent, in the other experiments in which insulin was withdrawn, either before or after hypophysectomy (see experiments 10 and 11).

At the conclusion of the above experiment thyroxine was discontinued and insulin administered in conjunction with cortisone daily for 21 weeks. Thereafter insulin was withdrawn for four days and a total of 0.642 g. of crude pituitary administered in equally divided doses over the four days. The total lipids, cholesterol, and lipid phosphorus, as well as the ketone bodies, increased to levels greater than those observed in the insulin-deprived depancreatized baboon before hypophysectomy (cf. experiments 13 and 10), but the blood sugar was not elevated to the extreme levels observed in the D.-H. baboons, B. 384 and B. 368, deprived of insulin and receiving only crude anterior pituitary gland (cf. experiment 13 with experiments 3 and 8). B. 386 became gravely ill and died one week later with an intensely fatty liver, despite the administration of cortisone.

Comment

Removal of the hypophysis from a depancreatized baboon does not correct the fundamental defect in carbohydrate metabolism. Moreover, the capacity of the baboon to maintain a hyperglycaemia for a variable length of time after hypophysectomy is dependent on the extent of residual adrenocortical activity. Long-standing hypophysectomy or an induced severe depression of the adrenal cortex following the administration and withdrawal of cortical hormones can lead to severe hypoglycaemia in depancreatized baboons not receiving insulin during short periods of starvation. In such instances the baboon is not apparently able to mobilize glucose from non-carbohydrate sources such as protein or fat, and the blood sugar continues to fall to very low levels. When fed carbohydrate the baboon develops hyperglycaemia, as does a depancreatized insulin-deprived baboon.

In all the experiments cited above, whether or not the baboons received hormone therapy, the severe lipaemia and the ketonaemia could be effectively controlled by the administration of adequate amounts of insulin. This does not mean that every lipaemia is the consequence of a relative or absolute insufficiency of insulin. It has been shown in our laboratory that: (1) thyroidectomy in baboons is associated with a variable lipaemia which can be controlled by thyroxine (van Zyl, 1956) as is the case in hypothyroidism of man (Boyd and Connell, 1936); (2) the administration of cortisone to hypophysectomized or stalk-sectioned baboons results in a moderately intense lipaemia which can be reduced either by withdrawal of cortisone or by the administration of thyroxine even though cortisone therapy be continued (van Zyl, 1956); (3) after the administration of crude anterior pituitary to normal baboons, all the lipid fractions tend to decrease without any accompanying change

in the blood sugar (unpublished data); and (4) castration leads to elevation of all the lipid fractions, which can be reduced by the administration of oestrogen.

In these several experimental situations where adequate supplies of insulin are available, it would appear that an elevation of the blood fats, without an associated ketonaemia, is a function in part at least of adrenocortical activity and some depression of thyroid function. However, the development of a severe ketonaemia is dependent on a measure of insulin deficiency in association with active secretion of somatotrophic hormone (S.T.H.). The regulation of the level of the serum lipids therefore depends, in part at least, on a dynamic relationship between insulin and adrenocortical and thyroid hormones, while the level of the blood ketones is dependent in the main upon a dynamic relationship between S.T.H., insulin, and to a less extent of thyroxine.

The marked individual differences in the degree of lipaemia and ketonaemia described in 15 baboons after

ketonaemia; (3) cortisone and thyroxine together restore the lipaemia and lead to a slight elevation of the ketone bodies; (4) crude human anterior pituitary alone grossly accentuates the hyperglycaemia, and causes a moderate lipaemia and ketonaemia more intense than that occurring in the diabetic baboon; (5) crude human anterior pituitary in conjunction with cortisone can reproduce the full diabetic picture, which may be even more severe than that observed in the depancreatized baboon before hypophysectomy; and (6) cortisone counteracts the extreme hyperglycaemia induced in insulin-deprived D.-H. baboons receiving crude human anterior pituitary gland.

In our opinion, these several experiments in the baboon may assist in the classification of diabetes on a biochemical basis, with particular reference to the levels of the total lipids, cholesterol, lipid phosphorus, ketone bodies, as well as of the glucose in the blood. The biochemical pattern in turn may disclose to some extent the nature of the endocrine participation in the disordered metabolism.

TABLE III.—Summary of Effects of Endocrine Therapy on the Lipids, Ketone Bodies, and Glucose in the Blood of Pancreatectomized and Pancreatectomized-hypophysectomized Baboons after a Four-day Period of Insulin Withdrawal

Expt. No.	Operation	Experimental Treatment	Total Lipids	Cholesterol	Lipid Phosphorus	Ketonaemia	Hyperglycaemia
1	P		+++	+++	+++	+++	+++
2	P+H		+ or ±	+++	±	+++	+++
3	P+H	Cortisone+crude pituitary	++++	++++	++++	+++	+++
4	P+H	Cortisone+crude pituitary+thyroxine	++++	++++	++++	+++	+++
5	P+H	Cortisone	+++	+++	+++	±	+++
6	P+H	Thyroxine	Normal	Normal	Normal	Normal	+++
7	P+H	Crude pituitary	+	+++ or ±	+++ or ±	+++	+++++
8	P+H	Cortisone+thyroxine	++++	++++	+++	±	+++

P=pancreatectomy. H=hypophysectomy. ± very mild, within normal range. + mild. ++ moderate. +++ severe. ++++ very severe.

pancreatectomy (Gillman *et al.*, 1958a) can be taken to reflect differences in the intensity of participation in metabolism of the adrenal cortex, pituitary, and thyroid in each baboon. When the hypophysis is removed from a depancreatized baboon the individual differences observed in the lipid fractions are minimized. Thus the cholesterol levels in five depancreatized baboons deprived of insulin for four days ranged from 175 to 540 mg./100 ml., whereas after the removal of the hypophysis, associated with a marked reduction in adrenocortical and thyroid activity, the range of the cholesterol values in these same baboons was reduced (152 to 236 mg./100 ml., Table I). Furthermore, by the administration of appropriate endocrine preparations to D.-H. baboons it was possible, in the absence of insulin, to exaggerate the cholesterolaemia (Table II, experiments 7 and 9).

In the terms of the experiments in D.-H. baboons receiving endocrine therapy it is suggested that severe lipaemia with a severe ketonaemia could be attributed to marked adrenocortical activity, active secretion of S.T.H., and possibly to moderate activity of the thyroid (Table III, experiments 3 and 4), while a severe lipaemia and a low ketonaemia might be due to pronounced adrenocortical activity and depressed secretion of S.T.H. (Table III, experiments 5 and 8). A low lipaemia and a low ketonaemia could be attributed to marked depression of the adrenal cortex and thyroid and a corresponding depression of S.T.H. (Table III, experiment 2). Attention is drawn to two additional biochemical patterns—namely, (1) a low lipaemia with a severe ketonaemia and severe hyperglycaemia (Table III, experiment 7), and (2) normal serum lipid levels and normal blood ketone bodies (Table III, experiment 6). The first was produced by crude pituitary in the absence of insulin and in the face of depressed adrenocortical and thyroid activity, and the second by intense thyroid activity with great depression of the adrenal cortex and in the absence of S.T.H.

From the experiments conducted in B. 368, B. 386, and B. 384, it can be concluded that in the D.-H. baboon deprived of insulin, (1) cortisone can restore the lipaemia but not the ketonaemia; (2) thyroxine prevents the development of a lipaemia, cholesterolaemia, phospholipaemia, and

Summary

Removal of the hypophysis from depancreatized baboons deprived of insulin did not alleviate the hyperglycaemia but did prevent the excessive lipaemia and abolish the ketonaemia. It was demonstrated in depancreatized-hypophysectomized baboons that by the administration of cortisone the hyperlipaemia, cholesterolaemia, and phospholipaemia could be raised to levels greater than those in the same animals before hypophysectomy, but was unattended by ketonaemia.

A saline suspension of acetone-dried human anterior pituitary administered to depancreatized-hypophysectomized baboons scarcely affected the serum lipids but did produce a severe ketonaemia and hyperglycaemia. The complete diabetic picture was reproduced in depancreatized-hypophysectomized baboons by cortisone in conjunction with crude human anterior pituitary.

From a consideration of the relevant data it was indicated that the individual differences in response to pancreatectomy were not only a function of the lack of insulin but of the intensity of participation of the adrenal cortex, of the thyroid gland, and of somatotrophic hormone in the metabolism of each baboon.

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