THE EFFECTS OF ADRENALECTOMY AND HYPOPHYSECTOMY UPON EXPERIMENTAL DIABETES IN THE CAT

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(Received for publication, December 20, 1935)

The possible participation of the adrenal glands in the series of events following pancreatectomy in animals has been the subject of numerous investigations. These fall into two main groups: (*a*) those in which the adrenal medulla was removed or its secretion paralyzed by section of the nerve supply to the gland before or after pancreatectomy, (*b*) those in which both adrenal glands were removed along with the pancreas. The order in which these different endocrine glands were excised has varied all the way from attempts to remove both adrenals and pancreas at one operation by Mayer (1) to the serial operations used by Hédon (2).

As the result of the first group of experiments there has accumulated the most convincing evidence that the withdrawal of epinephrine from the body either by removal of the adrenal medulla or section of its nerves does not in any way modify the effect of a subsequent pancreatectomy (3–8).

It is obvious that great difficulties confront the attempt to remove both adrenal glands and the pancreas, and these difficulties are reflected in the results of many published experiments. Until recently the short survival and moribund condition of such preparations has rendered almost useless any observations that have been made. Stewart and Rogoff (4) have severely criticized all experiments made up to 1922 which purported to show some interrelationship between these endocrines, but it must be stated that their conclusion that the adrenals do not influence pancreatic diabetes is not supported by their own experiments, since their totally adrenalectomized and depancreatized dogs lived only a few hours.

Turcatti (5) has prepared 11 totally adrenalectomized and depancreatized dogs. The operations were carried out in various orders. The shortest survival was $5\frac{3}{4}$ hours and the longest 40 hours. Nevertheless, this author concludes that simultaneous removal of all adrenal and pancreatic tissue prevents the usual hyperglycemia. The paper of Viale (10) appears to be a recitation of the experiments of Turcatti (5). In another paper by Lewis and Turcatti (9) one adrenal and the pancreas were removed and the dogs maintained with insulin. Upon removal of the last adrenal all insulin was withdrawn. Of 11 dogs prepared in this manner the shortest survival was 11 hours and the longest 72 hours. Since but little change occurred in the blood sugar and as glycosuria persisted, the authors concluded that total adrenalectomy under these conditions was of no value in the alleviation of pancreatic diabetes.

The introduction of adrenal cortical extracts capable of maintaining life in totally adrenalectomized animals has been utilized by two groups of workers. Leloir (8) has prepared 4 dogs in the manner used by Lewis and Turcatti, but after removal of the last adrenal and the withdrawal of insulin the dogs were injected with a cortical extract prepared by the method of Swingle and Pfiffner. The longest survival was 3 days, too short a time to throw any light upon the influence of adrenalectomy in experimental diabetes.

While our work was in progress Hartmann and Brownell (11) published a preliminary report upon 7 cats that were totally adrenalectomized and depancreatized in stages. 2 died within 24 hours and the others were treated with cortin. Of these one died in 4 days without much reduction in the diabetes, another in 8 days, probably as the result of an insulin injection. Of the remaining 3, one died in 6 days during which period it exhibited lowered blood sugar and slight glycosuria. Another lived 13 days and exhibited some reduction in the diabetes. The last animal survived for 38 days and the authors state that for 3 weeks no reduction in the diabetes was observed, but after this a marked amelioration was found. It is obvious that the survival of a totally depancreatized cat for this period is quite exceptional. The authors conclude that cortin is necessary for the development of the full diabetic condition.

Throughout this work we have endeavored to make a quantitative comparison of several aspects of the diabetic syndrome following pancreatectomy in normal, hypophysectomized and adrenalectomized animals. We have been fortunate in being able to prepare a sufficient number of doubly operated animals whose period of survival and general condition warranted studies upon their metabolism and hence have not had to base our conclusions, as so many workers have done, upon animals which survived only for a few hours after operation.

Methods

Cats have been used in the experiments described. The reasons for using this species are: (*a*) the cat was the animal most readily available for pancreatectomy; (*b*) surgery is easy for mechanical reasons; and (*c*) because cats seem relatively resistant to shock and infection.

In all types of operation nembutal (pentobarbital sodium) has been the anesthetic. The intraperitoneal dose for the normal cat is 50 mg. per kilo. In operating on previously hypophysectomized or adrenalectomized animals, 30 mg. per kilo is sufficient. These animals must be anesthetized with great care.

All operations have been performed under strict aseptic technique except in the case of transbuccal hypophysectomies. Pancreatectomy has been done by dissection with fine forceps. In one series of animals two stage pancreatectomy was done by the removal of all but the splenic tip at a first operation, the remnant being removed subsequently.

Adrenalectomy, usually done through the lumbar approach, is very easy in the cat and needs no comment.

In addition to removal of the adrenals two other types of adrenal operation have been performed: (*a*) Denervation of the adrenal. After recovery from right adrenalectomy the left adrenal was exposed and the splanchnic nerve cut. The adrenal ganglion was also doubly ligated and cut. (*b*) Demedullation of the adrenals. After recovery from right adrenalectomy the left adrenal is denervated as above and the upper pole of the gland cut off. The adrenal medulla is then destroyed by a dental drill. The operation has been described by Houssay and Lewis (3) and others.

Hypophysectomy in the cat has been described by McLean (12), Allan and Wiles (13) and McPhail (14). We have used the buccal route, essentially as described by the above authors. The danger of infection is negligible. We have not used bone wax in the sphenoid opening and only the palate requires catgut sutures.

McPhail does not refer to unsuccessful hypophysectomy and it is worth mentioning that of the 11 fatalities occurring in 33 cats following buccal hypophysectomy, 7 were due to hypoglycemia on the 5th to 17th day. Meningitis occurred only once, accidental hyperpyrexia killed 2, and one had a large clot in the fossa. The surviving 22 cats were depancreatized. Of these 8 died from various causes soon after the operation. In other words, 14 animals, or 42 per cent, survived these two operations long enough to be considered successful preparations.

Care of Animals.—When first obtained, the animals have been kept and well fed in an isolation room for 1 to 2 weeks to reduce the incidence of respiratory infections. After first stage operations (first adrenalectomy or hypophysectomy) they have been kept in single cages which were carefully cleaned, and fed unmeasured amounts of raw beef and fish. Animals after pancreatectomy, with or without other operations, have been kept in metabolism cages and fed measured diets. The diets have been 40 gm. raw pancreas and 100 gm. of canned salmon, liver or beef daily. These diets have been varied at times and any food not eaten has been weighed and the actual intake determined. Water was supplied *ad lib.* These diets will maintain normal cats in good health. The animals were weighed at suitable intervals. The urine has been collected for each 24 hour period, preserved with toluol and kept in an ice box until the chemical studies were completed.

Chemical Methods.—Quantitative urine sugars have been done by Benedict's method and the results checked at intervals by the Shaffer-Hartmann method. Urine nitrogen has been determined by the micro Kjeldahl method and urine ketones as described by Van Slyke. Blood was obtained from the ear veins and analyzed for glucose by the Benedict micro method. Blood for urea analyses may be obtained in the same manner.

Autopsy Findings.—All animals have been carefully autopsied and especial search made for pancreatic tissue. In the animals considered in this paper none was found.

In the adrenalectomized-depancreatized cats the presence of accessory cortical tissue was looked for. In only one animal out of 17 reported in this paper was any found. This cat (No. 2-20) will be referred to later.

The contents of the pituitary fossa of the 6 hypophysectomized-depancreatized cats described here were examined microscopically for hypophyseal tissue. In 3 animals fragments of the posterior lobe were found. In no case was any anterior lobe tissue present.

The Maintenance of Adrenalectomized Cats with Cortical Extracts

We have found that large amounts of cortical extract in terms of dog units a day are necessary to maintain adrenalectomized cats in good health.

In the present work we have used extracts from six sources. These were eschatin—Parke, Davis (10 dog units per cc.); a preparation of Dr. G. A. Harrop (50 dog units per cc.); an extract prepared by Dr. J. J. Pfiffner (60 dog units per cc.); a cortical extract supplied by Dr. G. F. Cartland of the Upjohn Company (130 dog units per cc.); an extract supplied by Dr. S. W. Britton (not assayed in dog units); and our own preparation by the Swingle and Pfiffner method (not assayed).[1]

It has been found that between 30 and 50 dog units per kilo of body weight per day are necessary under the conditions present in our laboratory to maintain adrenalectomized cats in good health. All the animals were adrenalectomized in two stages. They did not receive any additional sodium salts with the diet. In some of the animals receiving a large number of dog units daily the adequacy of the replacement therapy is well shown by the fact that they lived in excellent health and were later successfully depancreatized.

Classification of the Animals Studied.—The animals reported in this paper fall into five main groups. None of these received any insulin except where specially noted, but all the adrenalectomized animals received cortical extract daily.

Group 1.—At a preliminary operation all but one-sixth of the pancreas was removed together with one adrenal gland. The remaining splenic portion of the

[1] We are indebted to Drs. O. Kamm, G. A. Harrop, J. J. Pfiffner, S. W. Britton and G. F. Cartland for generous supplies of these extracts.

pancreas was either transplanted under the skin of the abdomen, or in some cases was left *in situ*. At a subsequent operation 10 to 34 days later the remainder of the pancreas and the second adrenal were removed. As controls upon this group other animals were subjected to similar procedures, except that at the completion of the pancreatectomy the remaining adrenal gland was left intact.

Group 2.—Total pancreatectomy was performed and the animals maintained by means of insulin and weighed diets. The adrenal glands were then removed in stages, insulin therapy being continued after the first adrenalectomy. After the second adrenalectomy all insulin was stopped. This method of preparing adrenalectomized-depancreatized animals has been the least successful of those that we have attempted, since all but one of the animals died within 3 or 4 days.

Group 3.—One adrenal was first removed. A week or 10 days later the second adrenal and the entire pancreas were removed. This operation is surprisingly well borne by the cat. 10 cats were operated upon in this manner.

As controls for this group we have used 10 cats, totally depancreatized in one stage, in which the adrenal glands were left intact. Furthermore, since there is a difference of opinion as to the effects of adrenal denervation and removal of the adrenal medulla upon pancreatic diabetes, we have depancreatized two further groups of 5 cats each. In the first group one adrenal was removed and the other denervated, in the second group one adrenal was removed and the medulla of the other gland drilled out, and the splanchnic nerve cut.

Group 4.—5 adrenalectomized cats maintained for various periods on cortical extracts prepared by different workers were depancreatized. One of these animals was exhibiting signs of adrenal insufficiency at the time of the pancreatectomy and died within 24 hours. The others were in excellent health and had held or gained weight since the total adrenalectomy.

Group 5.—Houssay and Biasotti (15, 16) have shown that a previous hypophysectomy greatly ameliorates the diabetes following pancreatectomy in the toad and dog. We have extended the number of species in which this effect is observed by depancreatizing 13 hypophysectomized cats. 4 of these died in diabetic coma following the injection of anterior pituitary extract (Squibb) at various times after pancreatectomy. One animal was also adrenalectomized, one killed for liver glycogen and in another cat the hypophysis was removed after the pancreas. The remaining 6 have been used for comparison with the totally adrenalectomized-depancreatized cats.

In assessing the effects of a given procedure upon pancreatic diabetes it is obvious that more than one criterion is desirable. Thus, prolongation of life is by itself not entirely acceptable especially if the period is only moderately extended. The individual variation may be so wide as to cast doubt upon the allegedly beneficial procedure. Nevertheless, if along with a moderate extension of the life span we find that the other stigmata of diabetes are also moderated, then we are justified in assuming that the procedure employed has produced an alteration in the characteristic metabolic picture that follows total pancreatectomy.

Consequences of Pancreatectomy

The response of these various groups of animals to pancreatectomy has been examined in the following particulars:

Survival.—In studies upon experimental diabetes mellitus, the depancreatized dog has been the animal usually employed. By comparison, but few observations have been made upon the response of the cat to sudden deprivation of insulin. It has been recognized that in this animal the period of survival is much less than in the dog. In a study of 12 cats Azodi (17) found the average survival to be 4 days with a range from 2 to 5 days. Loewi (18) and Epstein and Baehr (19) observed a similar span of life after total pancreatectomy. Ring and Hampel (20) have remarked upon the rapidity and severity of diabetic acidosis and ketosis in this species following pancreatectomy.

Table I shows that the average survival of cats deprived of insulin is about 4 days. The manner in which this insulin deprivation is brought about does not appear to affect the survival period. Thus, cats acutely depancreatized or those in which a pancreatic remnant is removed, or those from which insulin therapy is abruptly withdrawn, all show an average survival of about the period stated. The extreme range of survival observed in any animals of this type is 2 to 8 days. In fact, 16 of the 19 animals in Table I, groups I A, II A and III A, were dead in 5 days or less.

Ring (21) has suggested that the amelioration of experimental diabetes produced by hypophysectomy or adrenalectomy might be attributed to the loss of weight suffered by the animals as a result of operations previous to the pancreatectomy. A study of Table I would indicate that this is not a factor in the cat. It is true that animals carrying a pancreatic transplant or those maintained upon insulin (Table I, groups I A and II A) lost about 20 per cent of their initial body weight before pancreatectomy. Nevertheless, when deprived of all insulin they did not survive longer than the animals in group III A in which total pancreatectomy was performed in one stage, when they were of normal weight.

Some workers have assigned to epinephrine an important rôle in the sequence of events that follows pancreatectomy. Indeed, Barnes and his coworkers (22) have recently published experiments which would indicate that removal of epinephrine from the organism by section of the splanchnic nerves or demedullation of the adrenals greatly ameliorates the diabetes following total pancreatectomy in the dog. Such animals are stated to survive longer and to exhibit a degree of glycosuria comparable to that found in the hypophysectomized-depancreatized dog. Results of this kind are in complete disagreement with

TABLE I

		No. of animals	Average weight loss		Survival	
			Before pancreatectomy	After pancreatectomy	Average	Range
			per cent	*per cent*	*days*	*days*
Group I	A. Pancreatic graft removed. Adrenals intact	3	18.0	9.0	3.3	2–5
	B. Pancreatic graft and both adrenals removed	6	22.0	5.0	8.7	6–12
Group II	A. Depancreatized. Insulin withdrawn	6	20.0	15.0	4.3	2–8
	B. Depancreatized, second adrenal removed and insulin withdrawn	3	12.0	9.0	6.0	4–8
Group III	A. Depancreatized. Adrenals intact	10	0.0	16.0	4.6	3–8
	B. Depancreatized. Adrenals denervated	5	3.0	23.0	6.6	3–12
	C. Depancreatized. Adrenals demedullated	5	8.0	21.0	5.0	2–7
	D. Pancreas and second adrenal removed	4	3.0	20.0	16.0	14–28
Group IV	Adrenalectomized, then depancreatized	4	2.0	20.0	18.0	11–25
Group V	Hypophysectomized, then depancreatized	6	5.0	40.0	48.0	35–85

those reported by other workers who have followed similar procedures on the dog (3–8).

In Table I, groups III B and III C, will be seen the effects of these operations upon the survival of depancreatized cats. It will be apparent that the slight increase in the survival period cannot be taken as evidence in support of the experiments of Barnes *et al.*, particularly as Table II shows that the severity of the diabetes as judged by other criteria was in no way abated.

When we consider the effects of a total adrenalectomy upon the survival of depancreatized cats we are drawn to the conclusion that it is the loss of the adrenal cortex rather than the medulla that is responsible for the amelioration of the diabetes observed.

Our first adrenalectomized-depancreatized cats, Table I, group I B, which were prepared by removal of a pancreatic transplant along with the second adrenal did not have a markedly increased period of survival. Nevertheless no animal died in less than 6 days and 2 survived for 12 days. It was, however, the striking changes in the glycosuria and ketonuria that led us to prepare animals whose condition had not been lowered by extensive preliminary operations.

In 10 animals the whole of the pancreas and the remaining adrenal were removed at the same time. 3 were sacrificed in good health for liver glycogen and fat determinations 5 days later. 2 animals developed serious wound infections and died in 7 and 9 days respectively, while one animal relapsed into diabetic coma and died, subsequent examination revealing a large accessory adrenal cortical body (No. 1-66).

The remaining 4 animals (cited in Table I, group III D and Table II F) had no complications of this character and it is apparent that in them the survival period has been significantly increased.

One animal, No. 1-69, was killed 28 days after pancreatectomy, another, No. 1-67, died 17 days later, while the remaining 2, Nos. 2-10 and 2-14, died 2 weeks after extirpation of the pancreas.

The last group of adrenalectomized-depancreatized cats (Table I, group IV, and Table II G) are those prepared by removal of the pancreas from adrenalectomized animals that had been maintained in good health upon cortical extracts. Cat 2-20 was maintained for 28 days after adrenalectomy upon a cortical extract.[2] Following pancreatectomy it survived for a further 19 days.[3] Cat 2-25 was treated with eschatin for 14 days before pancreatectomy and survived 11 days after pancreatectomy. Cat 2-36 was treated for 7 days with an extract,[4] then depancreatized. It survived 16 days. Finally, cat 2-39 was in good health 9 days after adrenalectomy and treatment with an extract prepared by us according to the method of Swingle and Pfiffner. When depancreatized it lived for another 25 days.

In view of the survival periods of the animals in groups III D and IV we are of the opinion that total adrenalectomy previous to or

[2] This extract was supplied by Dr. J. J. Pfiffner.

[3] This cat was found at autopsy to possess a small cortical body 1 mm. in diameter.

[4] This extract was kindly supplied by Dr. S. W. Britton.

synchronous with total pancreatectomy increases the survival period of the cat over that usually observed in the animal depancreatized with adrenal cortical tissue left intact.

As in the dog, hypophysectomy previous to pancreatectomy is followed by very long survival periods. The average of our 6 Houssay cats (Table I, group V and Table II E) was 48 days, one animal surviving almost 3 months. These periods far exceed those found in the adrenalectomized-depancreatized cats, but factors at present not understood may be operating to shorten life in the latter.

Behavior and Mode of Death.—It has long been recognized that the usual mode of death of depancreatized dogs is in diabetic coma, attended by acidosis. This is not an invariable rule, since greatly emaciated animals may die of inanition without coma, not however, without exhibiting gross glycosuria and some ketonuria prior to death.

It may be categorically stated that none of our adrenalectomized-depancreatized nor hypophysectomized-depancreatized cats spontaneously developed diabetic acidosis, ketosis or coma, in striking contrast to the depancreatized animals in which this sequence of events is an almost invariable occurrence. Thus, out of 29 cats deprived of insulin, either by pancreatectomy or withdrawal of this substance subsequent to pancreatectomy, 26 relapsed into coma before death, of the remaining animals the death of one could probably be attributed to peritonitis following the removal of a pancreatic transplant, while the other 2 died of inanition 8 to 12 days after operation, not, however, without first exhibiting the same perversion of metabolism as was observed in the greater number.

This immunity to acidosis and ketosis that is so characteristic of the doubly operated animals is reflected in their improved appetite and behavior. The depancreatized cat rarely eats except during the first 24 or 48 hours after operation. As soon as ketone bodies appear in the urine food is refused and the animal gradually becomes apathetic and slips into a comatose condition. On the other hand, the appetite of the doubly operated animals is at first very poor, and all food may be refused for several days. In good preparations the ingestion of food is then resumed and, in fact, they often exhibit the voracious appetite seen in depancreatized animals maintained upon insulin. This is particularly so in the case of the hypophysectomized-depancreatized cats; but the adrenalectomized-depancreatized group as a rule have rather poor appetites.

All the doubly operated animals lost weight even when consuming amounts of food adequate to maintain normal animals (Table I). The degree of weight loss was proportional to the length of survival and in the case of the hypophysectomized-depancreatized animals may reach 40 per cent of the initial value before death occurs. These animals ultimately succumb to inanition partly as a result of the mild diabetes that persists and partly as a result of the factors introduced by the loss of the external pancreatic secretion.

In the adrenalectomized-depancreatized animals death has frequently occurred suddenly, often when the animals had lost but little weight and were eating well. The high incidence of hypoglycemic attacks in these animals has led us to suspect this factor as the cause of these often unexpected demises. Our reasons for supposing that these hypoglycemic episodes were not entirely due to a deficiency of the water and salt metabolism hormone of the adrenal cortex will be considered later.

Glycosuria, Nitrogen and Ketone Body Excretion.—(*a*) *During Fasting.*—In the fasting depancreatized animal the blood sugar remains elevated while glucose continues to appear in large amounts in the urine. In addition, the urinary nitrogen excretion is elevated two or threefold above that found in the normal fasting animal. Even more characteristic is the presence in the urine of acetone bodies, often in large amounts. That these phenomena are found in the fasting depancreatized cat is demonstrated in Table II B, C and D. It will be observed that the glucose excretion is about 3 gm. per kilo of body weight a day, while the urinary nitrogen is doubled or trebled as compared to that found in normal cats during similar fasting periods. The ketonuria is very marked, while the D/N ratio, although by no means constant from animal to animal, is set at a high level.

The animals in Table II C and D leave no doubt that the extirpation of the adrenal medulla or paralysis of its secretion by nerve section does not prevent the appearance of the characteristic high levels of glucose, nitrogen and ketone body excretion, following pancreatectomy.

Cat 1-65, Fig. 1, illustrates the difference between the effects of adrenal denervation and total adrenalectomy upon pancreatic diabetes in the same animal

The right adrenal was removed on Oct. 5, 1934, and the left adrenal denervated on Oct. 24. Total pancreatectomy was performed on Oct. 31 and no insulin was administered. In spite of fasting the glycosuria promptly rose to a high level

TABLE II

Glucose, Nitrogen and Acetone Body Excretion of Various Cats during Fasting

Cat No.	Days after pancreatectomy	Glucose	Nitrogen	Acetone	D/N
		A. Normal			
	days	*g/k/d**	*g/k/d**	*mg/k/d**	
1-77	Fasting 5	—	0.6	9	—
1-85	" 7	—	0.6	—	—
1-86	" 7	—	0.4	—	—
2-03	" 7	—	0.7	10	—
2-04	" 7	—	0.6	15	—
2-05	" 6	—	0.8	23	—
2-06	" 6	—	0.7	—	—
Average.........................			0.6	15	—
		B. Depancreatized—Adrenals Intact			
1-73	1st–3rd	3.0	1.1	28	2.8
1-76	1st–3rd	3.7	1.6	102	2.3
1-87	1st–3rd	2.2	1.0	85	2.2
2-00	1st–5th	2.9	1.4	275	2.1
2-47	1st–4th	4.2	1.7	174	2.4
Average.........................		3.2	1.4	133	2.4
		C. Depancreatized—Adrenals Denervated			
1-95	1st–9th	3.4	1.1	64	3.0
2-03	1st–12th	2.3	1.3	84	1.9
2-05	1st–7th	3.0	1.1	220	2.8
2-07	1st–3rd	3.4	1.0	230	3.5
Average.........................		3.0	1.1	150	2.8
		D. Depancreatized—Adrenal Medullae Removed			
1-98	1st–6th	2.7	1.2	125	2.2
1-99	1st–3rd	2.3	1.2	100	1.9
2-01	1st–6th	2.5	1.3	83	1.9
Average.........................		2.5	1.2	103	2.0
		E. Hypophysectomized and Depancreatized			
1-40	1st–4th	1.3	0.9	7	1.6
1-83	1st–6th	0.8	0.6	5	1.4
2-22	32nd–34th	0.3	0.5	—	0.6
2-26	1st–3rd	0.5	0.6	12	0.8
Average.........................		0.7	0.7	8	1.1
		F. Simultaneous Adrenalectomy and Pancreatectomy			
1-67	2nd–4th	0.7	0.6	15	1.2
1-69	4th–6th	0.1	0.4	6	0.3
2-10	1st–4th	0.1	0.4	2	0.3
2-14	1st and 2nd	0.3	0.9	—	0.3
2-15	1st–3rd	0.4	0.5	—	0.8
2-21	1st–3rd	0.0	0.5	20	—
2-25A	1st–4th	0.5	0.7	12	0.7
Average.........................		0.3	0.6	11	0.5
		G. Adrenalectomized and Then Depancreatized			
2-20	1st–3rd	1.1	0.7	11	1.6
2-25	2nd–4th	0.3	0.5	7	0.6
2-36	1st–4th	0.8	0.7	9	1.1
2-39	2nd–4th	0.4	0.7	9	0.6
Average.........................		0.7	0.7	9	1.0

* Signifies grams or milligrams per kilo of body weight a day.

and 24 hours later marked acetonuria was present. The institution of insulin therapy and dietary control promptly led to a diminution in the glycosuria and a disappearance of the acetonuria. On Nov. 7 the left adrenal was removed and insulin withdrawn. During the ensuing week, glycosuria was very slight and acetonuria did not appear. 8 cc. of a potent cortical extract prepared by Swingle and Pfiffner's method were injected daily.

As Houssay and Biasotti (23) have pointed out, the most striking effects of hypophysectomy upon pancreatic diabetes are the changes observed in the endogenous protein metabolism. In confirmation of this Table II E shows that not only is the glucose excretion greatly

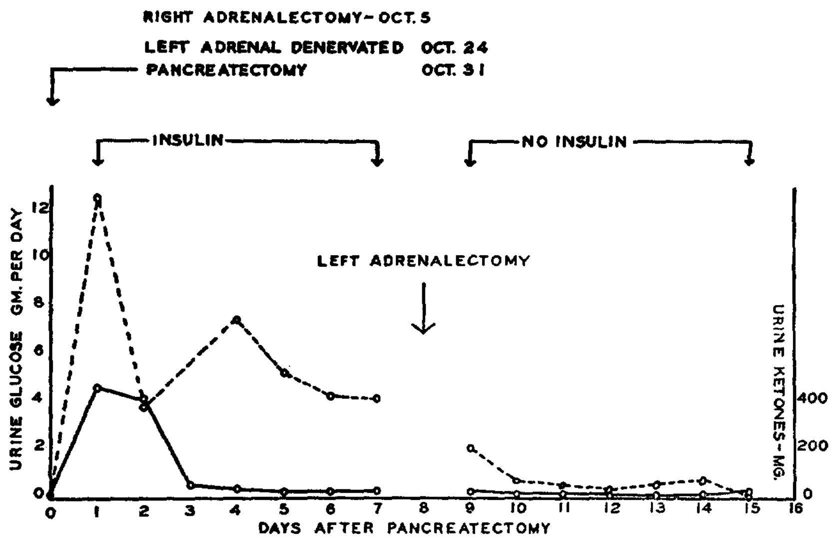

FIG. 1. Cat 1-65. The negative effect of adrenal denervation and the marked effects of total adrenalectomy upon pancreatic diabetes. Dotted line represents urine glucose, the full line urine ketone bodies. For details see text.

reduced but the nitrogen excretion is restored to the normal fasting level in the hypophysectomized-depancreatized cat. Even more characteristic is the absence of ketosis and acidosis as is indicated by the slight urinary excretion of the ketone bodies. The removal of the main factors participating in the development of diabetic coma must account in large part for the increased survival of the animals.

Table II F and G shows that the effects of adrenalectomy upon the fasting diabetic metabolism are identical with those of hypophysectomy. There is the same marked reduction in the urinary excretion of glucose, nitrogen and ketone bodies, and it is difficult to avoid the conclusion that both these procedures are producing their effects by interference with the same phases of the diabetic metabolism.

(*b*) *On a Constant Diet.*—Table III contains the results of studies made upon (*a*) normal, (*b*) hypophysectomized-depancreatized, and (*c*) adrenalectomized-depancreatized cats when fed for several days upon a meat diet of 100 gm. of canned salmon and 40 gm. of raw pancreas a day. The glucose excretion of the well fed hypophysectomized-depancreatized cats is still slightly below that of the fasting depancreatized animals, while the nitrogen excretion is at about the same level.

TABLE III

Glucose, Nitrogen and Ketone Excretion while Eating 40 Gm. Pancreas and 100 Gm. Salmon Daily

Cat No.	Days after pancreatectomy	Glucose	Nitrogen	Ketones	D/N
A. Normal					
	days	*g/k/d*	*g/k/d*	*mg/k/d*	
1-41	16 day period	—	1.5	13	—
1-68	8 " "	—	1.7	15	—
Average			1.60	14	
B. Hypophysectomized and Depancreatized					
1-40	13th–32rd	1.7	1.0	7	1.7
1-60	4th–20th	2.3	1.3	7	1.8
2-22	21st–31st	3.2	1.6	12	2.0
2-30	5th–14th	1.6	1.3	—	1.2
Average		2.20	1.30	9	1.9
C. Adrenalectomized and Depancreatized					
1-67	6th–16th	1.6	1.2	6	1.3
2-10	5th–13th	0.5	1.0	4	0.5
Average		1.05	1.10	5	0.9

Blood Sugar Level and Hypoglycemic Episodes.—In the depancreatized cat the fasting blood sugar is almost invariably greater than 200 mg. per cent. In the terminal stages of coma it rises to exceedingly high levels, values exceeding 500 mg. per cent being not uncommon.

Houssay and Biasotti (15) have called attention to the fluctuating character of the blood sugar level in hypophysectomized-depancreatized dogs and have noted that actual hypoglycemic episodes occasionally occur. Our own experience with similarly operated cats in general supports these findings. When such cats are fasted, not only may the glycosuria disappear, but the blood sugar may fall to such low levels that death from the resulting hypoglycemia occurs. This was the case in 2 cats in our series. In well fed animals wide fluctuations in the fasting level also occur from day to day, even when the food intake remains constant. Curiously enough, the amount of glycosuria of such an animal with constant dietary intake is much more uniform, and it would appear that the fasting blood sugar level is subject to marked variation depending upon the length of time elapsing since the last meal. It has been recognized that the fasting hypophysectomized animal is often subject to a fatal hypoglycemia, but it is remarkable that even the complete absence of the pancreas does not always protect it against this circumstance.

The untreated adrenalectomized cat is very prone to exhibit a lowered blood sugar level even before the grosser signs of insufficiency are present (24). Terminal hypoglycemic symptoms are of common occurrence in such animals. The usual view that has been taken is that the marked reduction in the blood sugar level is associated with the absence of the cortical hormone, together with the refusal of food that invariably occurs a few days before death. Furthermore, it has been noted that the injection of glucose, although increasing the blood sugar and effecting some temporary improvement, does not prolong the lives of such animals more than a few hours. Of particular interest in this respect are the recent observations of Harrop, Soffer, Nicholson and Strauss (25). These authors report that adrenalectomized dogs maintained in excellent health by the injection of the cortical hormone or by the use of ample sodium chloride and bicarbonate feedings relapse into severe hypoglycemia when fasted for a few days. Such animals are at once restored to good health by glucose injections. It is obvious that these experiments raise the question as to whether the hypoglycemia commonly observed in adrenal insufficiency is to be attributed to the lack of the cortical hormone controlling water and salt metabolism or whether it is to be looked upon as evidence of an associated disturbance in carbohydrate metabolism brought about by removal of the adrenal glands, and not compensated for by the injection of amounts of extract capable of controlling other manifestations of adrenal insufficiency.

These remarks are prompted by our observation that the adrenalectomized-depancreatized cat is even more prone to hypoglycemic episodes than is the hypophysectomized-depancreatized animal. Thus, out of 18 adrenalectomized-depancreatized cats, 5 developed such severe hypoglycemia that glucose injection was necessary to save their lives. It should also be emphasized that these animals lived for several days after such hypoglycemic episodes, which is evidence that the low blood sugar level in these instances was not associated with severe adrenal insufficiency, not only because cortical extract was being injected, but also by the established fact that glucose only temporarily resuscitates animals suffering from severe adrenal insufficiency. An example will illustrate this:

Protocol of Cat 2-39

Right adrenalectomy May 16th. Weight 2.5 kilos.
Left adrenalectomy May 25th. Weight 2.5 kilos.
Maintained in excellent condition for 9 days by 4 cc. daily of cortical extract.
Pancreatectomy June 3rd. Weight 2.5 kilos.
Killed June 28th. Weight 1.7 kilos. Survival 25 days.

Date	Meat eaten	Urine glucose	Blood sugar	Cortical extract	Notes
	gm.	*gm.*	*mg. per cent*	*cc.*	
June 17	65	1.8	226	6	
" 18	0	0.9	13	6	Very weak, relieved at once by 3 gm. glucose
" 19	90	3.6	246	6	
" 20	60	1.0	212	6	
" 21	20	0.0	173	10	
" 22	90	1.4	104	10	
" 23	60	2.5	—*	10	Very weak, relieved at once by 3 gm. glucose
" 24	115	2.9	118	10	
" 25	98	1.7	28	10	Mild symptoms relieved by 50 cc. milk
" 26	50	Lost	—	10	
" 27	0	Trace	63	10	
" 28	Animal killed				

Terminal serum urea nitrogen 66 mg. per cent. Terminal serum CO_2 combining power 41 volumes per cent. Liver glycogen 1.0 per cent. Liver fatty acids 9.4 per cent.

* Too weak to read.

Carbohydrate Tolerance. (*a*) *Injected Glucose.*—Houssay and Biasotti (23), Biasotti (26) and Barnes and Regan (27) have stated that in contrast to the depancreatized animal the ingestion of glucose by the hypophysectomized-depancreatized dog is followed by a lowered blood sugar curve and that considerable quantities of the ingested glucose are retained.

TABLE IV

Glucose Tolerance Tests

Cat No.	Days after pancreatectomy	Glucose	Method of administration	Blood sugar						Notes
				Before	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	
A. Hypophysectomized—Depancreatized										
	days	*gm.*		*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	
1-57	21	1.5	Intraperitoneally	37	149	138	118	—	—	In shock at onset
2-22	9	3.0	"	206	326	340	318	—	328	
2-22	50	3.0	"	140	282	308	380	324	312	
2-27	4	3.0	"	210	394	416	388	392	372	
B. Adrenalectomized—Depancreatized										
8-6	2	3.0	Mouth	68	—	152	—	—	—	
8-6	8	3.0	"	32	88	86	90	—	—	In shock
1-17	1	3.0	"	138	—	—	340	—	—	
1-09	2	3.0	"	104	171	147	115	—	—	
9-8	7	2.5	Intraperitoneally	18	—	—	—	—	134	In shock
1-17	4	3.0	"	28	—	—	—	—	104	" "
1-09	4	3.0	"	42	226	225	232	219	217	
2-10	14	3.0	"	30	—	133	—	—	—	In shock
2-15	4	3.0	"	184	344	326	298	—	272	
2-21	4	3.0	"	240	272	300	332	340	314	
2-39	15	3.0	"	13	—	119	111	—	123	In shock

Table IV contains the results of our experiments with glucose feeding or intraperitoneal injection into hypophysectomized-depancreatized and adrenalectomized-depancreatized cats.

As will be observed, in six instances the glucose was administered as the animals were exhibiting various degrees of hypoglycemic shock. Since this invariably occurred as a result of fasting, they represent the effect of glucose upon the blood sugar under these conditions. The remaining figures were obtained by administering glucose to the animals after an overnight fast.

It will be apparent that when the initial blood sugar level in the animals that we have tested is below 40 mg. per cent, the response to glucose is essentially normal, whereas if the blood sugar level is elevated above the normal level, a typically diabetic response is obtained. In interpreting this condition it should be noted that the animals with low blood sugar levels were in varying degrees of prostration, often with subnormal body temperatures. As a consequence, it is possible that the absorption of the administered glucose was delayed. Since the condition of such animals was almost at once improved by the glucose, and as they did not subsequently excrete it even when observed for many hours, it is difficult to avoid the conclusion that when these hypoglycemic episodes occur the utilization of considerable quantities of ingested glucose is possible even in the complete absence of the pancreas.

Quite a different picture is presented when glucose is administered to doubly operated animals in good health and with elevated initial blood sugars. From an observation of a considerable number of such animals we are of the opinion that when the fasting blood sugar is elevated these animals are clinically in their best condition, and at this time the administration of glucose gives a blood sugar response indistinguishable from that found in totally depancreatized animals.

(b) *Addition of Glucose to a Constant Diet.*—From the results in Table IV it would be expected that the addition of glucose to the diet of animals in good health would result in its almost quantitative excretion. This has been carried out in the case of two hypophysectomized-depancreatized cats, both of which survived for over 50 days after pancreatectomy and ate 100 gm. of canned salmon and 40 gm. of pancreas daily. After a suitable fore period 3 gm. of glucose were added to each of the two daily meals for 3 days. This was readily consumed, but, in both cases practically a quantitative excretion was observed. Since the animals were excreting 4–7 gm. of glucose daily during the fore period, this result is not surprising.

(c) *Utilization of the Glucose Derived from a Meat Diet.*—It has long been recognized that when a completely phloridzinized or depancreatized dog is fed upon a protein and fat diet, a constant ratio between urine glucose and nitrogen is established. In the depancreatized cat, before the development of severe acidosis, this ratio is 2.8.

Houssay and Biasotti (29) have demonstrated that the urinary D/N ratio of the hypophysectomized-depancreatized dog is much less than the values established for the totally depancreatized animal. A study of these ratios in our cats indicates that these low values are also found in the adrenalectomized-depancreatized cats (Table II).

If we know the amount of urine nitrogen excreted and if we assume that in the doubly operated cats the same proportion of protein is converted into glucose, we are in a position to calculate the quantity

TABLE V

Utilization of Glucose by Hypophysectomized-Depancreatized and Adrenalectomized-Depancreatized Cats as Calculated from Urinary Glucose and Nitrogen Excretion

Cat No.	Food daily	Period	Average urine nitrogen per day	Average urine glucose per day	Available glucose Urine $N_2 \times 2.8$	Glucose retained	Glucose retained
A. Hypophysectomized—Depancreatized							
		days	*gm.*	*gm.*	*gm.*	*per cent*	*g/k/d*
2-22	40 gm. pancreas, 100 gm. salmon	11	3.4	6.7	9.5	29.5	1.3
2-30	" "	10	3.5	4.3	9.8	56.1	2.1
1-40	" "	20	2.8	4.8	7.8	38.5	1.1
1-60	" "	17	3.2	5.8	9.0	35.6	1.3
1-83	Fasting	6	2.1	2.9	5.9	51.0	0.8
2-22	"	3	0.9	0.5	2.5	80.0	1.0
2-26	"	3	2.2	1.8	6.2	71.0	1.3
B. Adrenalectomized—Depancreatized							
1-67	40 gm. pancreas, 100 gm. salmon	11	2.3	3.0	6.5	54.0	1.8
2-10	" "	9	3.7	1.8	10.4	82.6	2.3
2-25A	Fasting	4	1.7	1.4	4.8	71.0	1.3
2-36	"	4	1.9	2.0	5.3	62.4	1.2

of glucose formed in the body by the metabolism of protein. This figure may then be compared with the actual glucose excretion. Any difference between the two should represent the glucose derived from protein that has been retained. Similar calculations can also be made for the fasting animal.

Table V contains the results of calculations made in this manner. It is apparent that in these doubly operated animals a large proportion of the glucose derived from protein is retained. In some animals this proportion may be over 80 per cent of the calculated amount. Nevertheless the actual amounts of carbohydrate utilized are very small (about 1–2 gm. per kilo a day) and it would appear that the capacity of the tissues of these animals to assimilate glucose derived from protein, although perhaps superior to that of the depancreatized group, nevertheless remains at a low level.

In conclusion, in view of these three different types of experiments, we are of the opinion that the carbohydrate tolerance of the depancreatized cat is but little improved by the removal of either the hypophysis or adrenals. We except from this statement the curious results obtained with animals in the hypoglycemic state in which it is obvious that other factors are operating.

The Influence of the Water and Salt Hormone of the Adrenal Cortex upon the Diabetes of Adrenalectomized-Depancreatized Cats

One question remains: To what extent are the effects of adrenalectomy upon pancreatic diabetes due to the loss of the cortical hormone controlling water and salt metabolism? Since the removal of this hormone is followed by marked metabolic disturbances it might be argued that the effects upon pancreatic diabetes are merely secondary to the deficiency of this hormone.

It has been demonstrated (28) that the cachexia of hypophysectomized rats is not relieved by cortical extracts adequate to maintain life in adrenalectomized dogs. Furthermore, the hypophysectomized dog does not exhibit any of the characteristic features of cortical insufficiency, yet there is no doubt as to the different character of experimental pancreatic diabetes in such animals. In addition, we have found that the glycosuria or ketonuria of hypophysectomized-depancreatized cats is unaffected by the injection of 100–300 dog units of the cortical extracts at our disposal.

Although these experiments demonstrate that hypophysectomy brings about an amelioration of pancreatic diabetes even when ample supplies of cortical hormone are present, they do not answer the possibility that a deficient supply of this substance may be responsible for the apparently equally effective results of adrenalectomy.

The following observations speak against this possibility.

(*a*) As Table VII shows, the effects of adrenalectomy upon pancreatic diabetes are well marked during the first 48 hours after simultaneous removal of both endocrine organs. Since the full effects of adrenal insufficiency are not manifest for several days it is considered unlikely that any loss of the water and salt hormone would be reflected upon the carbohydrate metabolism at such an early date.

(*b*) All the adrenalectomized-depancreatized animals received large amounts of this cortical hormone in terms of dog units daily. We have already pointed out the necessity for these large doses in the cat, and while it is true that some of our earlier animals were probably inadequately treated this was not the case for all of them. Thus, while the average daily dose given to the adrenalectomized-

TABLE VI

Type of animals	No. of animals		Cortical extract	Total base	Chlorides	CO_2 combining power	Urea nitrogen	Glucose	Cholesterol	Dry weight
			*du/k/d**	*m.-eq.*	*m.-eq.*	*vol. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*gm. per cent*
Normal	5	Average...	—	159	121	43	28	108	80	7.3
		Range.....	—	156–162	117–126	39–48	24–35	95–115	38–115	7.0–7.6
Depancreatized	11	Average...	—	147	98	24	81	592	132	8.9
		Range.....	—	127–159	78–118	15–38	17–150	338–1050	57–162	7.3–11.2
Adrenalectomized and showing marked symptoms	2	Average...	None	135	104	26	74	79	135	9.0
		Range.....	—							
Adrenalectomized and depancreatized	12	Average...	28	150	108	37	53	179	101	8.5
		Range.....	18–47	135–165	98–122	21–50	30–84	30–308	42–200	7.2–9.5
Hypophysectomized and depancreatized	4	Average...	—	156	119	45	45	207	132	7.6
		Range.....	—	154–159	114–122	31–50	29–52	40–320	69–197	6.1–10.0

All the analyses in this table have been carried out by Dr. F. W. Sunderman of this department.

* Signifies dog units per kilo a day.

depancreatized cats in Table I, groups I and II, was only 18 dog units (range 8–37), we can detect no difference (except length of survival) in the amelioration of the diabetes between these animals and those in groups III and IV which received an average daily dose of 28 dog units (range 18–47) of cortical extracts prepared by the method of Swingle and Pfiffner.

(*c*) Animals suffering from a deficiency of the water and salt controlling hormone of the adrenal cortex exhibit characteristic alterations in the electrolyte pattern of their serum.

In Table VI we have averaged the electrolyte values of the serum of cats that have undergone various operations. In all cases the blood was collected under oil from the anesthetized animal after the survival periods indicated in Table I. This period was short in the depancreatized or adrenalectomized animals and relatively long in the adrenalectomized and depancreatized or hypophysectomized and depancreatized groups.

The figures demonstrate that in the hypophysectomized-depancreatized group there is but little alteration in the electrolyte pattern, again emphasizing the point that an inadequate supply of cortical extract is not a prerequisite for the alleviation of the diabetes observed in hypophysectomized animals. However, in the adrenalectomized-depancreatized cats in spite of the large amounts of cortical extract given, there is on the average a small diminution in the total base

TABLE VII

The Glucose, Nitrogen and Acetone Body Excretion of Adrenalectomized-Depancreatized Cats Receiving Large Amounts of Cortical Extract

	No. 2-56, adrenalectomized				No. 2-58, adrenalectomized				
Days after pancreatectomy	1	2	3	4	1	2	3	4	5
Cortical extract, *dog units*	1040	520	650	650	1040	260	260	650	650
Meat eaten, *gm.*	20	85	70	110	0	0	25	55	100
Glucose, *gm. per kilo*	0.5	1.3	1.1	1.0	1.5	0.7	0.5	1.1	1.8
Nitrogen, *gm. per kilo*	1.7	1.1	1.0	1.5	0.7	0.7	0.5	0.8	1.3
Acetone bodies, *mg. per kilo*	0	17	15	11	4	5	3	4	9
D/N	0.3	1.2	1.1	0.7	2.1	1.0	1.0	1.4	1.4
	No. 2-61, adrenalectomized				No. 2-47, adrenals intact				
Days after pancreatectomy	1	2	3	4	1	2	3	4	5
Cortical extract, *dog units*	1300	910	650	650	0	0	0	0	
Meat eaten, *gm.*	55	40	40	50	0	0	0	0	
Glucose, *gm. per kilo*	1.2	0.6	0.8	0.8	3.8	3.8	4.2	1.6	Died
Nitrogen, *gm. per kilo*	1.4	0.6	0.6	0.7	1.7	1.7	1.5	0.6	
Acetone bodies	0	9	10	4	148	148	251	25	
D/N	0.8	1.0	1.3	1.1	2.2	2.2	2.8	2.7	

with a somewhat larger decrease in the serum chloride, together with an increase in the blood urea and some degree of hemoconcentration. It is apparent that towards the end of their survival certain animals have developed some degree of insufficiency, others, to the contrary, have retained a practically normal serum pattern. As we have mentioned before, we have been unable to differentiate these animals by the degree of glucose or acetone body excretion.

(*d*) One of the most cogent arguments against a deficiency of the water and salt hormone as the reason for the amelioration of diabetes in adrenalectomized cats is the animals in Table II G. These were maintained in good health by cortical extracts for periods from 7–28 days before pancreatectomy. The amelioration of the diabetes that followed was of the same extent as that observed in animals in which the adrenalectomy and pancreatectomy were performed in one stage.

Since the above was written we have recently studied 3 additional adrenalectomized-depancreatized cats to which large amounts of a very potent cortical extract[5] were administered. One of these animals (No. 2-61) was adrenalectomized and maintained in good health for a month before pancreatectomy. The other 2 animals (Nos. 2-56 and 2-58) had the remaining adrenal and all the pancreas removed at one operation. The daily glycosuria, nitrogen excretion and ketonuria along with that of a depancreatized cat are given in Table VII. The degree of amelioration of the diabetes was as great as that previously observed, although one animal received three times the amount of cortical extract that had been sufficient to maintain it before pancreatectomy.

DISCUSSION

The data presented indicate that the removal of the hypophysis or adrenal glands modifies in all its aspects the sequence of events that usually follows total pancreatectomy in the cat. Not only is the survival of these animals significantly increased, but death, when it ultimately occurs, is not preceded by a period of severe acidosis and ketosis. Even more significant is the fact that during life the characteristic and extreme perversions of metabolism are greatly modified. In brief, either hypophysectomy or adrenalectomy convert the diabetes from a severe, rapidly fatal form into one of moderate degree in which inanition rather than acidosis is the ultimate cause of death.

These modifications are expressed by:

1. The virtual abolition of ketosis and acidosis. It is the removal of these factors that is undoubtedly responsible for the prolongation of life. Of even greater importance is the manner in which this alteration is produced. There are at least three possibilities: (*a*) The rate and amount of fat mobilized into the liver and there metabolized may be greatly reduced. This is supported by some preliminary observations in which we have found that the usual intense fatty infiltration of the liver of depancreatized cats does not occur in the same length of time in the doubly operated animals. Nevertheless, over longer periods some fatty infiltration does take place and at autopsy in animals surviving for long periods all the body stores of fat are utilized. (*b*) In animals without pituitary or adrenals the complete oxidation

[5] This extract was prepared by Dr. Cartland of the Upjohn Co.

of acetone bodies may be possible, particularly if they are not delivered to the tissues in the usual excessive amounts. Along classical lines it might be argued that sufficient oxidation of carbohydrates has been resumed to effect this utilization. Our present findings, however, indicate that the utilization of carbohydrate is but little improved by these procedures. (*c*) Finally, it is possible in these doubly operated animals that fat metabolism follows a pathway not involving the formation of these ketone bodies.

2. The excessive conversion of the body protein is greatly reduced in the doubly operated animals. As a result, during fasting, the glycosuria falls to very low levels and is associated with a corresponding reduction in nitrogen excretion. This protein sparing effect can again hardly be attributed to the resumption of sufficient carbohydrate oxidation since all our present evidence is to the contrary.

3. This persistence of a markedly impaired carbohydrate metabolism together with a reduction in the intensity of protein and fat metabolism indicates that the probable effect of hypophysectomy or adrenalectomy upon pancreatic diabetes is a diminution in the production of glucose and ketone bodies, rather than a restoration of carbohydrate oxidation. All the evidence indicates that normal carbohydrate oxidation is impossible in the complete absence of insulin.

It is generally agreed that it is the removal of the anterior portion of the hypophysis that is responsible for the effects produced by a total hypophysectomy. The evidence we have presented here, together with the results previously reported, would seem to establish the fact that the removal or paralysis of the secretion of the adrenal medulla is without effect upon the results of a total pancreatectomy. The effects of adrenalectomy must therefore be due to the ablation of the cortical portion of the gland. It appears to us that removal of the adrenal cortex may produce an amelioration of pancreatic diabetes in three possible ways.

1. In spite of the experiments we have cited in Table VII, the water and salt hormone of the cortex was not supplied in sufficient quantity for the diabetes to develop in its usual manner when the pancreas was removed (11).

2. Removal of all cortical tissue might produce alterations in the function of the anterior pituitary of such a nature that its diabetogenic

activity is no longer exerted. In other words, a functional suppression of this organ is brought about by total adrenalectomy. We are engaged at present in testing this hypothesis.

3. The apparently identical effects of adrenalectomy and hypophysectomy might be related by reason of the trophic control that the anterior pituitary exerts over the adrenal cortex. Thus, following hypophysectomy there occurs a marked atrophy of the adrenal cortex, and it is tempting to speculate as to whether the effects of hypophysectomy upon pancreatic diabetes are not mediated by the ensuing occurrence of cortical atrophy. If this explanation is correct then the adrenal cortex plays an essential part in the increased protein and fat catabolism following pancreatectomy.

It is becoming apparent that the anterior pituitary hormones play an important rôle in those conditions under which gluconeogenesis is increased. Thus it has been found (15) that hypophysectomized dogs rapidly develop hypoglycemia when fasted. Furthermore, if such animals are phloridzinized, the glucose, nitrogen and acetone body excretion is greatly diminished compared to that found in the normal animal (29, 30).

Under similar conditions adrenalectomized animals also exhibit marked deviations from the normal. Thus Harrop *et al.* (25) have demonstrated that adrenalectomized dogs exhibit marked hypoglycemia after a short fast, even though they have continued to receive amounts of either cortical extract or sodium salts sufficient to maintain them in good health when fed. Evans (31) has recently found that when adrenalectomized rats either maintained on salt or cortical extract are phloridzinized the excretion of glucose, nitrogen and acetone bodies is much reduced, again emphasizing the identical effects of hypophysectomy and adrenalectomy in a condition in which gluconeogenesis is particularly concerned.

Furthermore, the curious findings of Evans (32) of the effects of exposure to low oxygen tensions upon the liver glycogen, nitrogen and acetone body excretion of the fasting white rat also support the above views. This author has shown in the normal fasted rat that exposure for 24 hours to an atmosphere containing 10.5 per cent oxygen results in a marked formation of liver glycogen. Since the glycogen content of the remainder of the body remains unchanged, this liver glycogen must have had its origin from non-carbohydrate sources and this is borne out by the finding of an increased nitrogen excretion under these conditions. Adrenalectomized or hypophysectomized rats when similarly treated show neither the increase in liver glycogen nor the excess nitrogen excretion, while on the other hand, animals in which only adrenal cortical tissue is left intact behave as do normal rats. Finally, the administration of large amounts of cortical extracts containing the hormone controlling water and salt metabolism is without effect in restoring to normal the response to these conditions. The mechanism by which low oxygen tensions produce these effects is unknown, yet one feature of the response to them is apparently a stimulation of gluconeogenesis. As before, this stimulus is ineffective if either the adrenal cortex or anterior pituitary is absent.

SUMMARY

1. The hypophysectomized cat shows an alleviation of the diabetes following pancreatectomy comparable to that previously demonstrated by others in the dog.

2. It is possible by various procedures to remove both adrenals and all the pancreas from cats. Such animals have survived for as long as 4 weeks without the use of insulin, the average survival being 18 days. Daily injections of cortical extract are necessary. By contrast, cats deprived of insulin by similar procedures but with adrenals intact survive only 4–5 days.

3. Adrenalectomized-depancreatized cats show as striking an alleviation of the diabetes as do those hypophysectomized and depancreatized. This is expressed by the markedly decreased glucose, nitrogen and acetone body excretion compared to that found in the depancreatized cat, as well as by the increased survival period.

4. Removal of epinephrine by denervation or demedullation of the adrenals does not protect against pancreatic diabetes in the cat.

5. The carbohydrate tolerance of depancreatized cats is not significantly increased by hypophysectomy or adrenalectomy.

The exceptions to this finding have all been in animals presenting varying degrees of spontaneous hypoglycemia.

6. It is our opinion that the effects of hypophysectomy or adrenalectomy upon pancreatic diabetes are due to diminution of the production of glucose and acetone bodies rather than to the resumption of normal carbohydrate utilization.

We are indebted to the Pepper Laboratory of the University Hospital and to Dr. I. T. Zeckwer of the Department of Pathology for the examination of our histological material. We would also like to acknowledge the assistance we have received from Miss A. Case, Miss E. G. Fry and Miss D. Quinn of this department.

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