with every chance of improvement without the use either of cooling or of the extracorporeal circulation, but the most important aim of modern surgery is the direct correction under vision of the adult mitral valve, and this can be attained only by some form of assisted circulation.

It may be that one way of progressing towards this aim of a dry adult heart for the routine performance of surgery on its interior may be the use of an assisted circulation to take over in successive cases more and more of the circulation.

Experience will show what amount of aortic flow per minute is required for the maintenance of an adequate coronary and carotid circulation, but previous experience with pressure perfusion of the clamped aorta in emergency, by quantities of blood per minute small in proportion to the output of the pump, suggests that the necessary flow may not in fact be particularly high. On this occasion a flow of 500 to 800 ml. was maintained for a total period of 97 minutes, and it might be estimated that in that time there was a total flow of 70 litres through the machine. Alternatively, it might be said that the patient's total volume of circulating blood passed through the machine about 15 times, or that, for 97 minutes, the machine was responsible for 20 to 30% of the total cardiac output.

Bleeding during and after the operation is the most serious problem which we have to face, but we prefer the risk of bleeding as we experienced it in this patient to the still greater risk of clotting around the tubes of the machine at some critical stage of operation during which the patient's life might depend upon the efficiency of the artificial circulation. It seems reasonably certain that the bleeding we experienced was due in the main to platelet loss, though the effect of operation, transfusion of foreign blood, and the machine on clotting function is highly complex, and other factors certainly operate too. Methods are being developed for the collection of fresh blood rich in platelets; even fresh blood, drawn by routine methods, loses a high proportion of platelets in collection.

All the data collected concerning the effect of the machine have not been presented here—much of the material cannot be fully analysed until a series of cases is available for study. The management of collecting devices and the drill for the timing of samples require a large team of medical and technical staff, and the arrangements and control of apparatus, especially collecting apparatus in an operating-room already occupied by a complex surgical team, have been the subject of prolonged study and experiment.

We wish to acknowledge our indebtedness to many colleagues and assistants who have been concerned in this work and in the management of the case here reported. To the cardiologists at Hammersmith Hospital, including Dr. J. F. Goodwin and Dr. R. I. S. Bayliss, we owe a great deal of day-to-day advice and the pre-operative investigation and management of patients who are considered for this and other forms of surgery. We are indebted for help and advice in our electrocardiographic studies to Dr. J. F. Goodwin and Dr. L. G. Davies. Dr. S. J. Baker, of the department of haematology, has given much time and thought to our problems of coagulation and haemorrhage. Dr. John Beard, anaesthetist for thoracic surgery in the Postgraduate Medical School and Hammersmith Hospital, has been a most important member of the operative team, and has collaborated most helpfully. Mr. Ralph Shackman and the staff of the Surgical Research Laboratories have given us constant help, and Mr. Gerald Rainbow and Miss Eva Bottoms particularly have been unwearied in the maintenance of the machine. With New Electrical Products Ltd. we have explored now for a long period, and very happily, the technique of liaison between surgical and technological research; and Mr. J. Brown of that company has not only devoted endless time and skill to the original construction of the machine but has attended and studied its performance in the operating theatre. A second phase of this prototype apparatus embodying improvements which the function of this machine has suggested is now under construction; the cost of its development is being borne by a grant from the Nuffield Foundation. We have had assistance from the National Research Development Corporation in our plans for the machine's development.

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INSULIN RESISTANCE FOLLOWING HYPOTHALAMIC LESIONS AND REMOVAL OF THE ADRENAL MEDULLA

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It has long been thought that insulin-resistant diabetes might be associated with the presence of an insulin antagonist (Himsworth and Kerr, 1940). Resistance to insulin has been shown to develop in intact animals after the injection of purified growth hormone (Young, 1950) and of cortisone (Campbell *et al.*, 1950) over periods of some days. The work of Bornstein and Park (1953) has shown that neither of these hormones is an insulin antagonist, but that both are necessary for the development in the intact animal of the insulin antagonism found in alloxan-diabetic rats. Bornstein (1953) found that the insulin antagonism was confined to a specific lipoprotein fraction of the serum of such rats. The serum from a human subject rendered hypoglycaemic by a large dose of insulin also exhibited insulin antagonism, while that from a normal human subject and from normal rats possessed no such activity.

Section of those pathways from the hypothalamus to the brain stem which mediate autonomic function produced no change in insulin sensitivity (Beattie and Chambers, 1953a), but when the adrenal medulla was removed from these rats they developed marked resistance to insulin. These experiments are described below.

Material and Methods

Male albino rats of a single strain and weighing between 200 and 250 g. at the start of the experiment were used. For five weeks before the experiments began they were kept at a constant environmental temperature of 29.5° C. Rats of the series 1 experiments were kept at this temperature throughout the experimental period. Rats of the series 2 experiments were kept at 29.5° C. until day 12 of the experiment, when they were transferred to a cooler environment with a mean temperature of 18° C.

The rats of each series were divided into four groups. Group A rats were unoperated controls. Group B rats had brain lesions inflicted on day 0. The adrenal medullary tissue was removed from the group C rats on day 7. Group D rats had brain lesions made on day 0 and the adrenal medullary tissue was removed on day 7. All rats were killed on day 21.

Each group of rats in series 1 was divided into four subgroups. The first subgroup was used to obtain resting blood-glucose and resting liver-glycogen values. The second subgroup was given an intraperitoneal (I.P.) injection of insulin (1 unit per kg. body weight) on day 21. Blood-

glucose concentrations were determined on blood samples taken before and 30 minutes after the injection. The third subgroup received an I.P. injection of glucose (1 mg. per g. body weight) on day 21. Blood-glucose concentrations were determined as in the previous group. Samples of muscle were taken before and 30 minutes after the injection, and a sample of liver also 30 minutes after the injection. These tissue samples were used to determine the glycogen content. The fourth subgroup received an injection of glucose and insulin at the above dose levels and by the same route. Samples of blood, muscle, and liver were taken as in the third subgroup. The rats of series 2 were used only to determine resting blood-glucose and liver-glycogen values and the response of the blood glucose to an injection of insulin. The insulin used in all the experiments came from the same batch and had been assayed for glucagon content.

The site of the brain lesions and the method of producing them have been described already (Beattie and Chambers, 1953b). The adrenal medulla was removed by incising the cortex and expressing the medulla by gentle pressure on the cortex. At the end of the experiment the glands were fixed and sectioned to confirm that no remnant of medullary tissue had been left within the gland.

The procedures at the end of the experiment were :

1. Food was withdrawn at 5 p.m. on day 20 but ample water provided.

2. Between 10 a.m. and 12 noon on day 21 the rats were anaesthetized by an I.P. injection of pentobarbitone sodium (40 mg. per kg. body weight).

3. When anaesthetized a blood sample (0.2 ml.) was withdrawn from the heart. The left gastrocnemius muscle was exposed, ligated near its origin, and a sample (approximately 0.4 g.) removed, avoiding any obvious tendinous tissue. After weighing on a torsion balance, the sample was dropped into 4 ml. of a hot (100° C.) solution of potassium hydroxide (30% w/v).

4. Immediately after removal of the muscle sample the injection of insulin, glucose, or glucose with insulin was given. The total volume of fluid injected did not exceed 0.6 ml. per 100 g. body weight.

5. Precisely 30 minutes after the injection a second blood sample was taken from the heart, and after its removal a sample of muscle was removed from the right gastrocnemius muscle and treated as before.

6. The abdominal cavity was opened and a sample of liver (approximately 0.4 g.) taken from the left lateral lobe and treated in the same way as the muscle samples.

Blood samples were deproteinized by the barium-zinc procedure and the glucose content was determined by the method of Nelson (1944). After the samples of muscle and liver had dissolved, the tubes were cooled and the glycogen precipitated by adding 7.2 ml. of absolute alcohol. After centrifuging, the supernatant fluid was discarded, and the precipitate dried and then dissolved in 10 ml. of distilled water. Glycogen was determined (as glucose) by the anthrone method of Seifter *et al.* (1950). The glycogen content of liver and muscle was expressed as grammes of glucose per 100 g. wet tissue.

Results

Effect of Insulin on Blood-glucose Level.—The mean resting blood-glucose concentrations were considerably lower in group D rats of both series than those of the other groups. Rats of group D in both series failed to show a hypoglycaemic response after the injection of insulin (Table I).

Muscle-glycogen Content.—The glycogen content of muscle was determined only on series 1 rats. Rats with brain lesions only (group B) had a resting content of glycogen which was not significantly different from that in the control group. After removal of the adrenal medulla (group C) the resting level of glycogen was lower in one set of experiments and equal to that of the control rats in another set. Group D rats had a resting content significantly lower than that of the control group (Tables II and III). After the injection of glucose the glycogen con-

TABLE I.—Changes in Blood-glucose Concentration Following Insulin Injection

Group	Operation	Series 1 Environmental temp. 29.5° C.				Series 2 Environmental temp. 18° C.			
		Blood Glucose, mg./100 ml. ± S.E.				Blood Glucose, mg./100 ml. ± S.E.			
		No. of Rats	Resting Level	30 min. after Insulin	Diff.	No. of Rats	Resting Level	30 min. after Insulin	Diff.
A	Control	6	119 ± 3.6	71 ± 4.4	-48	8	96 ± 5.9	64 ± 4.9	-32
B	Lesions	5	100 ± 5.0	63 ± 3.3	-37	11	98 ± 4.0	46 ± 3.8	-52
C	Adrenal medulla removed	10	111 ± 5.2	71 ± 5.5	-40	10	115 ± 5.8	58 ± 3.3	-57
D	Lesions and adrenal medulla removed	7	60 ± 1.6	69 ± 9.2	+9	7	73 ± 4.1	89 ± 8.2	+16

Insulin dose, 1 unit per kg. body weight given intraperitoneally.

TABLE II.—Changes in Blood-glucose Concentration and Glycogen Content of Muscle and Liver After Injection of Glucose in Series 1

Group	Operation	Blood Glucose Mean ± S.E. mg./100 ml. Blood			Muscle Glycogen Mean ± S.E. g./100 g.		Liver Glycogen Mean ± S.E. g./100 g.
		No. of Rats	Resting Level	30 min. after Glucose	Resting Level	30 min. after Glucose	After Glucose
A	Control	7	104 ± 6.5	156 ± 7.2	0.635 ± 0.008	0.691 ± 0.010	1.346 ± 0.107 (0.962)
B	Lesions	4	110 ± 5.9	145 ± 5.7	0.652 ± 0.009	0.684 ± 0.006	1.436 ± 0.129 (1.178)
C	Adrenal medulla removed	4	102 ± 5.1	162 ± 7.9	0.515 ± 0.008	0.541 ± 0.006	0.840 ± 0.064 (0.658)
D	Lesions and adrenal medulla removed	4	84 ± 4.7	104 ± 4.9	0.468 ± 0.004	0.458 ± 0.007	0.213 ± 0.024 (0.120)

Dose of glucose, 1 mg. per g. body weight given intraperitoneally. Values in parentheses under the mean glycogen content of liver are mean resting values from Table IV.

TABLE III.—Changes in Blood-glucose Concentration and Glycogen Content of Muscle and Liver After Injection of Glucose and Insulin in Series 1

Group	Operation	Blood Glucose Mean ± S.E. mg. 100 ml. blood			Muscle Glycogen Mean ± S.E. g. 100 g.		Liver Glycogen Mean ± S.E. g./100 g.
		No. of Rats	Resting Level	30 min. After Glucose and Insulin	Resting Level	30 min. After Glucose and Insulin	After Glucose and Insulin
A	Control	7	109 ± 5.6	92 ± 5.2	0.736 ± 0.011	0.750 ± 0.009	1.463 ± 0.098 (0.962)
B	Lesions	4	100 ± 4.1	79 ± 3.8	0.687 ± 0.007	0.705 ± 0.010	1.397 ± 0.077 (1.178)
C	Adrenal medulla removed	3	106 ± 5.0	84 ± 4.8	0.690 ± 0.011	0.736 ± 0.009	0.948 ± 0.089 (0.658)
D	Lesions and adrenal medulla removed	4	104 ± 3.9	124 ± 5.2	0.519 ± 0.008	0.497 ± 0.011	0.248 ± 0.027 (0.120)

Dose of glucose, 1 mg. per g. body weight. Dose of insulin 1 unit per kg. body weight. Values in parentheses under the mean glycogen content of liver are mean resting values from Table IV.

tent of muscle rose by almost the same amount in groups A, B, and C, but that of group D remained unchanged (Table II). When insulin and glucose were given the glycogen content rose again in groups A, B, and C, but not in group D. The blood-glucose levels fell in groups A, B, and C, but rose in group D by the same amount as it had when glucose alone was given (Table III).

Liver Glycogen.—The resting glycogen content of the liver in series 1 rats was not significantly different in groups A and B. The mean content in group C was significantly lower than that of groups A and B. Rats of group D had

a very low content equal to about 15% of that in the control group. After exposure to cold conditions for nine days all liver glycogen values were markedly reduced. Group C rats again had a lower mean content than the control group and those of group D an extremely small amount (Table IV).

TABLE IV.—*Resting Glycogen Content of the Liver- and Blood-glucose Levels*

Group	Operation	No. of Rats	Series 1 Environmental Temp. 29.5° C.		Series 2 Environmental Temp. 18° C.	
			Blood Glucose Mean ± S.E. mg./100 ml.	Liver Glycogen Mean ± S.E. g. 100 g.	Blood Glucose Mean ± S.E. mg./100 ml.	Liver Glycogen Mean ± S.E. g./100 g.
A	Control	8	111 ± 5.3	0.962 ± 0.042	96 ± 5.9	0.073 ± 0.010
B	Lesions	8	103 ± 4.7	1.178 ± 0.061	98 ± 4.0	0.073 ± 0.008
C	Adrenal medulla removed	8	106 ± 5.7	0.658 ± 0.037	115 ± 5.8	0.045 ± 0.005
D	Lesions and adrenal medulla removed	8	78 ± 4.9	0.120 ± 0.008	73 ± 4.1	0.011 ± 0.004

All determinations were made on day 21 of the experiment. Series 2 rats had been exposed for 9 days to an environmental temperature of 18° C. from day 12 to day 21.

Body-weight Changes.—The differences between the mean weight at the start of the experiment and that on day 21 are given in Table V. Series 1 rats all showed an increase in weight which was not significantly different between

TABLE V.—*Changes in Body Weight During the Experimental Period*

Group	Operation	Series 1 Environmental Temp. 29.5° C.		Series 2 Environmental Temp. 18° C.	
		No. of Rats	Mean Change of Weight ± S.E. g.	No. of Rats	Mean Change of Weight ± S.E. g.
A	Control	28	+24 ± 7.6	16	+20 ± 5.2
B	Lesions	21	+20 ± 5.8	19	1 ± 4.2
C	Adrenal medulla removed	25	+22 ± 8.6	18	+5 ± 9.6
D	Lesions and adrenal medulla removed	23	+13 ± 11.7	15	-7 ± 10.1

The change in body weight is the difference between the weights of rats on day 0 and those on day 21.

groups. The control rats of series 2 had the same overall weight increase as the corresponding group in series 1. Rats of groups B and C maintained their starting weight, and those of group D showed a slight fall below the weight at the beginning of the experiment.

Discussion

Rats of series 1 (kept at 29.5° C.), which had brain lesions and were without any adrenal medullary tissue, showed no hypoglycaemic response after the injection of insulin and were unable to increase the glycogen content of muscle either in the presence of a slight hyperglycaemia following the injection of glucose or when insulin was given with glucose. Rats with either no adrenal medullary tissue or with brain lesions responded to these various injections of insulin, glucose, and insulin with glucose in the same way and to the same degree as the control rats. The glycogen content of the liver in rats on whom both operations had been done was much reduced. These findings suggest that an insulin antagonist was present in the rats with brain lesions and without adrenal medullary tissue, and that this antagonist was probably inhibiting the hexokinase system.

Bornstein and Park (1953) found that the insulin antagonism shown by the serum of alloxan-diabetic rats was

reversible by insulin in a concentration of 0.1 unit per ml. in the medium in which the isolated diaphragm from a normal rat was suspended. If the test muscle was taken from an alloxan-diabetic rat and suspended in serum from such a rat then insulin in this concentration failed to produce complete reversal of the insulin antagonism. Krahl (1951) had already pointed out that reversal of insulin antagonism was possible, provided there was enough insulin available. In the present experiments insulin was given in a dose of 1 unit per kg. body weight. Assuming that all the insulin was distributed over the extracellular fluid of the rat, and that this space forms about 28% of the weight of the rat, then the maximum concentration of insulin in the fluid bathing the muscle cells could not have exceeded 0.1 unit per 28 ml. if the insulin were evenly distributed throughout the space. It was probably much less. Rats of groups A, B, and C responded to this low concentration of insulin by increasing the muscle glycogen content, but the rats of group D did not. It would appear, therefore, that the insulin resistance exhibited by rats of group D would require an extremely high concentration of insulin for its reversal.

Bornstein and Park (1953) demonstrated that the presence of both growth hormone and cortisone was essential for the development of insulin antagonism in the serum of the hypophysectomized and alloxan-diabetic rat. If either or both hormones were added to normal serum no insulin antagonism was developed in that serum. If the insulin antagonism found in the rats of group D was of the same type as that found by Bornstein and Park, it would require both hormones for its development. The data in Table V leave no doubt that rats kept at 29.5° C. with brain lesions and with no adrenal medulla were able to increase their weights over a period of 21 days. It may be presumed, therefore, that these rats produced growth hormone at a rate at least as great as that of normal rats. These rats, too, showed no evidence of adrenal cortical deficiency, and normal cortical tissue was found in all the adrenal glands examined. It is reasonable to infer that these rats were producing, in quantities at least sufficient for normal existence, both corticotrophin (A.C.T.H.) and adrenal cortical steroids. Thus there is reason to believe that the two hormones necessary for the production of insulin antagonist of the Bornstein and Park type were present in rats of group D.

The mere differences in body weights recorded on day 0 and on day 21 do not give a true picture of the pattern of weight change. When brain lesions of the type inflicted in the present experiments are made there is a loss in body weight of about 20 g. during the first four days after the operation. This loss is made good by the end of the ninth day (Beattie and Chambers, 1953b). Removal of the adrenal medulla is followed by weight loss of about the same amount and is repaired in about the same time. Rats in group D thus repaired a total post-operative weight loss of about 40 g., and in addition increased their body weight by 13 g. above that on day 0. The true increment of weight in group D rats during 21 days was thus about 53 g., as compared with a weight increase in control rats of about 24 g.

Rats exposed to cool conditions (18° C.) react to these conditions by increasing heat production. Normal rats increased their oxygen consumption by 8%, those with brain lesions by 13.5%, rats without adrenal medulla by 15%, and rats without adrenal medulla and with brain lesions by 22% (Beattie and Chambers, 1953c). Thus after single operations (groups B and C) a weight loss of about 20 g. was repaired in spite of an increased oxygen consumption of 13.5–15%. The rats of group D regained almost all the weight loss after the two operations in spite of a rise in oxygen consumption of 22%. It would therefore not be unreasonable to presume that the rate of growth-hormone production, and probably also that of adrenal cortical steroids in the group D rats, was greater than that in normal rats under the same environmental conditions.

The exact role of the hypothalamus in the control of production of growth hormone and of corticotrophin (A.C.T.H.) is still obscure. Information derived from the effects of lesions in experimental animals and from the effects of tumours in man is equivocal. For example, Spirtos (1954) found that moderate-sized lesions of the hypothalamus (area unspecified) were followed by increased insulin sensitivity which could be countered by injections of growth hormone. Paton and Petch (1954) reported hyperglycaemia, a diabetic type of glucose-tolerance curve, and reduced sensitivity to insulin in a human subject in whom a brain tumour involving the hypothalamus (area unspecified) was discovered at necropsy. It would be valueless to attempt to explain the present findings in terms of hypothalamic function when such a conflict of evidence exists.

The interest of the present experiments lies in the fact that insulin resistance was produced in rats without destruction of pancreatic islet tissue and without the continued injection of hormones. Moreover, no direct damage was caused to the cell masses of the hypothalamus by the division of the fibre tracts leading from the hypothalamus to the brain stem. Late chromolytic changes were seen in certain cell masses which could with certainty be attributed to the section of the efferent fibres from them. Neither of the two operative procedures used in the production of insulin resistance had any demonstrable effect on insulin sensitivity. The insulin resistance which followed when both operations were done on the same rats was present 21 days after infliction of the brain lesions and 14 days after removal of the adrenal medulla. It is therefore improbable that the insulin resistance could be due to some irritative action set up by the operative procedures.

If the insulin resistance induced in these rats were due to the presence of an insulin antagonist—and the evidence is consistent with this assumption—then the possibility that insulin-resistant diabetes might arise from a cause or causes which do not involve primarily either the pancreas or the pituitary gland must receive serious consideration.

Summary

After section of the pathways from the hypothalamus to the brain stem and removal of the adrenal medulla, rats kept at an environmental temperature of 29.5° C. showed no fall in the blood-glucose level 30 minutes after the injection of insulin in a dose of 1 unit per kg. body weight. Removal of the adrenal medulla alone or section of the hypothalamic pathways produced no change in insulin sensitivity.

The resting content of glycogen in muscle (gastrocnemius) was significantly lower than normal in rats with the hypothalamic lesions and without adrenal medullary tissue. The glycogen content did not rise after the injection of glucose (1 mg. per g. body weight) or after the simultaneous injection of glucose and insulin. The glycogen content of the liver was markedly reduced (15% of normal) in the resting state. When such rats were exposed to cold for nine days they still displayed no hypoglycaemic response to the injection of insulin. The glycogen content of the liver in the resting state was reduced to 11 mg. per 100 g. of liver.

The experimental data suggest that the insulin resistance found in these rats was due to the presence of an insulin antagonist.

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THE OCCURRENCE OF ELECTROCORTIN IN HUMAN URINE

BY

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The discovery by Grundy, Simpson, and Tait (1952) of a new hormone, called electrocortin,* which has the ability to increase both sodium retention and potassium excretion by the kidney, must inevitably give a new impetus to the study of the many conditions associated with sodium retention in man.

In recent years several workers have found evidence of the occurrence in certain human urines of a substance having the power to increase sodium retention by the kidney; but careful analysis of extracts of such urines by modern chromatographic methods has failed to reveal any evidence of the presence of deoxycortone, the only steroid hitherto known to possess such sodium-retaining properties in marked degree. It now seems likely that the sodium-retaining effects observed by earlier investigators were due to the presence in the extracts of this new hormone, electrocortin.

Most of the original observations suggesting the presence of a sodium-retaining principle in urine were made by Deming and Luetscher (1950). Using a method of bioassay on young adrenalectomized rats, they found that chloroform extracts of some human urines had the power, when injected, of reducing sodium excretion by the kidney. Under the conditions of their test deoxycortone acetate in doses of 5 to 25 µg. per rat had a similar effect, but larger doses of extract did not give greater sodium retention. In their earlier experiments evidence for the existence of a sodium-retaining substance in normal urine was equivocal, but a significant degree of activity was found in extracts of the urine of five out of eight patients with cardiac failure. In one patient with nephrosis a high titre of activity was also found. An extension of these observations was reported by Luetscher *et al.* (1952), who then found that the titre of sodium-retaining substance was high in the oedematous stage but fell to normal levels after diuresis with elimination of the oedema.

In 1953 Singer and Venning also found some evidence of sodium-retaining activity in extracts of nephrotic urine, and McCall and Singer (1953) found a sodium-retaining substance in eight out of nine nephrotic chil-

*The chemical formula of electrocortin has just been published by Simpson, Tait, Wettstein, *et al.* (*Experientia*, 1954, **10**, 132). It proves to be a steroid similar to corticosterone, but with an aldehyde grouping on C 18.