Thomas Addison's monograph of 1855 opens with the words: "It will hardly be disputed that at the present moment the functions of the suprarenal capsules, and the functions they exercise in the general economy, are almost or altogether unknown." Like so much of his writing, these words are still true. We have accumulated a mass of facts, but we still can say little about the influence of adrenal hormones in the general economy of the organism. Perhaps we must await the appearance of a second Thomas Addison to unlock a new door through which fresh ideas may flow. Let us hope that he will be recognized as readily as the genius of Thomas Addison was appreciated when, in 1824, he was appointed assistant physician to Guy's Hospital and began his long and fruitful career.

REFERENCES

- Addison, T. (1855). *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules*. S. Highley, London.
- Bayliss, W. M., and Starling, E. H. (1902). *J. Physiol.*, **28**, 325.
- Bernard, C. (1850). *C.R. Acad. Sci., Paris*, **31**, 371.
- (1853). *Nouvelle fonction du foie*. Baillière, Paris.
- (1855). *Leçons de Physiologie expérimentale appliquée à la Médecine*. Baillière, Paris.
- Brown-Séquard, G. E. (1856). *C.R. Acad. Sci., Paris*, **43**, 422, 542.
- Harris, G. W. (1948). *Physiol. Rev.*, **28**, 139.
- Hench, P. S. (1950). *Proc. roy. Soc. Med.*, **43**, 769.
- Hopkins, F. G. (1938). *Ergebn. Vit. Hormonforsch.*, **1**, v.
- Houssay, B. A., and Lewis, J. T. (1923). *Amer. J. Physiol.*, **64**, 512.
- Ingle, D. J. (1950). *J. clin. Endocrinol.*, **10**, 1312.
- Sheppard, R., Oberle, E. A., and Kuizenga, M. H. (1946). *Endocrinology*, **39**, 52.
- and Thorn, G. W. (1941). *Amer. J. Physiol.*, **132**, 670.
- Oliver, G., and Schäfer, E. A. (1894). *J. Physiol.*, **16**, Proc. i.
- Pavy, F. W. (1854). *Proc. roy. Soc. Lond.*, **7**, 371.
- (1860). *Ibid.*, **10**, 528.
- (1861). *Philos. Trans.*, **150**, 595.
- Rolleston, H. D. (1936). *The Endocrine Organs in Health and Disease*. Oxford Univ. Press, London.
- Swingle, W. W., and Piffner, J. J. (1929). *Anat. Rec.*, **44**, 225.
- (1930). *Science*, **71**, 321.
- Thorn, G. W., Engel, L. L., and Lewis, R. A. (1941). *Science*, **94**, 348.
- Vogt, M. (1943). *J. Physiol.*, **102**, 341.
- (1947). *J. Endocrinol.*, **5**, lvii.
- (1950). *British Medical Journal*, **2**, 1242.
- Wilks, S., and Daldy, R. M. (1868). *A Collection of the Published Writing of the Late Thomas Addison, M.D.* New Sydenham Soc., London.
- Young, F. G. (1936). *Ann. Sci.*, **2**, 47.

The National Association for Mental Health is often asked by parents to arrange for institutional care for young mentally defective children, frequently mongols (*Mental Health*, Winter, 1951, p. 21). Sometimes these applications are received from maternity hospitals on behalf of almost newborn infants. In many cases, however, the association is not in favour of this early removal because of the very distressing effect such an act frequently has upon the parents, who are often told the child is mentally defective and advised to send him away from home without any preparation or explanation being given. Sometimes, too, it may take months before accommodation can be found; such vacancies as exist should be reserved for really urgent cases. They point out that in cases showing no pronounced stigmata of mental defect it is almost impossible to arrive at a reliable prognosis at an early age, and the risk of mistaken decision, which may have serious consequences for the child, should not be overlooked. Most medical schools pay too little attention to the subject of mental deficiency—particularly in its ethical and social aspects—and the association wishes to stress this and the fact that there are few postgraduate openings in this field. Another urgent need is for mental deficiency clinics in outpatient departments. It has also been suggested that mentally deficient children under school age should be reported to local health authorities. The editor of *Mental Health* invites readers' opinions on these views—at Maurice Craig House, 39, Queen Anne Street, London, W.1.

PLASMA INSULIN IN HUMAN DIABETES MELLITUS

BY

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AND

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This paper summarizes our investigations on human diabetics, made by estimating the available insulin in their plasma. This is arrived at from the hypoglycaemic effect produced when their plasma is injected into specially prepared rats very sensitive to insulin. Our earlier publications (Bornstein, 1950; Bornstein and Trehwella, 1950, 1951; Bornstein and Lawrence, 1951) have aroused enough interest both in the technique and in the results to merit this further description. The plasma insulin results of 37 diabetics and 14 normal controls are now reported in tables, with comments and discussion.

Experimental Methods and Techniques

The method evolved by one of us (J. B.) (Bornstein, 1950; Bornstein and Trehwella, 1950) has been used throughout. Available plasma insulin is measured by injecting 1 ml. of plasma into special rats and observing for one hour the change in their blood sugar. These adults rats (called ADHA rats) are first made diabetic by an appropriate dose of alloxan. Then the hypophysis and both adrenals are removed, so that the animals become very sensitive to insulin and show a clear hypoglycaemic effect after even 1/20,000 of a unit, or 0.05 milliunit, the term used in this paper. It is obvious that such a rat presents difficulties in its preparation, its maintenance, and its standardization for the actual hour's blood-sugar test.

Standardization before Tests

(a) It is first essential to determine the conditions under which the blood-sugar concentrations of the ADHA rats are constant enough for the period of one hour necessary for an insulin assay. We should point out that different strains of rats vary considerably, and that temperature and diet control have to be closely investigated to obtain stable blood-sugar conditions. In all recorded experiments the rat environment temperature has been 27° C. In our experience bread soaked in milk—that is, readily assimilable carbohydrate—is the best standardizing diet. These rats were therefore freshly fed for one and a half hours in the morning with bread soaked in milk, and this food was then removed for one and a half hours before the start of the test. Tables I–IV show a satisfactory stability from the third to the fifth hour after the feeding procedure, and insulin assays were made from the third to the fourth hour.

(b) Next, after the injection of 0.5 and 1 ml. of saline, a series of *mock assays* were undertaken to test the stability of blood sugar and the absence of a spontaneous fall. These are shown in Tables II, III, and IV. Rats showing instability were rejected.

*Working under a travelling grant from the National Health and Medical Research Council of Australia.

TABLE I.—Mean Blood Sugar (mg./100 ml.) of ADHA Rats After Feeding

No. of Rats	Before Feeding	Hours After Feeding for 1½ Hours Only							
		1	2	3	4	5	6	7	8
7	124	236	205	179	179	178	164	143	113
8	94	196	168	142	139	141	127	116	87
8	116	228	181	132	130	131	121	91	78

The blood sugar was stable from the third to the fifth hour after feeding in these 23 rats. The third to fourth hour was the experimental time in all experiments.

TABLE II.—Mock Assay; Six ADHA Rats

Dose	Blood-Glucose Concentration		
	Start	1 Hour	Diff.
0.5 ml. normal saline	185	182	-3
	168	165	-3
	161	167	+6
	136	127	-9
	169	167	-2
	155	160	+5
Means ..	162	161	-1

TABLE III.—Mock Assay; Six ADHA Rats

Dose	Blood-Glucose Concentration		
	Start	1 Hour	Diff.
1 ml. normal saline	171	162	-9
	143	147	+4
	183	192	+9
	167	167	0
	128	126	-2
	138	134	-4
Means ..	155	154.7	-0.3

TABLE IV.—Mock Assay; 24 ADHA Rats

Dose	Mean Blood-Glucose Concentration		Diff. and Standard Deviation
	Start	1 Hour	
1 ml. normal saline ..	157	156	-1 ± 4.66

Fifteen animals showed a slight fall in blood glucose; nine animals showed a slight rise in blood glucose.

(c) With such selected ADHA rats a standard curve to graded doses of insulin was constructed. Animals of one size must be used or allowance be made for varying sizes. It was possible to construct standard curves over a range of 0.05 to 0.5 milliunit of insulin (Bornstein, 1950; Bornstein and Lawrence, 1951).

TABLE V.—Diabetic Patients Showing No Insulin in Plasma

Patient	Sex	Age	Fasting Blood Sugar (mg./100 ml.)	Ketosis	Weight	Plasma Insulin in milliunits/ml.	Later Diminution of Insulin Sensitivity of Test Animals
1	F	41	401	Not known	Losing	0	Yes
2	F	64	196	"	"	0	"
3	M	28	308	Present	"	0	"
4	M	42	298	Not known	"	0	"
5	F	37	256	Present	"	0	"
6	M	52	374	Not known	"	0	"
7	F	47	212	"	"	0	"
8	M	36	248	Present	"	0	"
9	F	52	313	"	"	0	"
10	M	32	402	"	"	0	"
11	F	9	406	"	"	0	No
12	M	28	168	"	"	0	Yes
13	M	42	212	"	"	0	No
14	F	5	356	"	"	0	"
15	M	17	368	"	"	0	"

(d) The untreated diabetic patients whose plasma insulin is reported (Tables V and VI) were also prepared to a standard. In the morning, instead of breakfast, 50 g. of glucose was given by mouth, and their blood

TABLE VI.—Diabetic Patients Showing Insulin in Plasma

Patient	Sex	Age	Fasting Blood Sugar (mg./100 ml.)	Ketosis	Weight	Plasma Insulin in milliunits/ml.	Later Diminution of Insulin Sensitivity in Test Animals
16	M	25	142	Absent	Slight loss	0.28	No
17	M	50	196	"	Obese	0.32	"
18	F	56	227	"	"	0.30	"
19	F	35	136	"	"	0.26	"
20	F	47	182	"	"	0.29	"
21	F	53	172	"	"	0.19	"
22	F	46	156	"	"	0.24	"
23	M	57	146	"	"	0.20	"
24	M	53	212	"	"	0.13	"
25	F	53	186	"	"	0.19	"
26	F	46	131	"	"	0.32	"
27	F	47	207	"	"	0.17	"
28	F	59	186	"	"	0.10	"

Mean plasma insulin = 0.23 milliunits/ml.

was collected two hours later, so as to stimulate any possible insulin secretion in a comparable way.

(e) *The Experiments.*—In six ADHA rats so prepared 1 ml. of quickly separated plasma from venous heparinized diabetic blood was injected. The change in their blood-sugar concentration one hour after injection constitutes the test, compared with the previous standard curve with varying doses of insulin. Four days later the sensitivity of these rats to two previously given doses of insulin was retested to determine whether the diabetic plasma had changed this sensitivity and to provide a check on the previous standard curve.

Results and Remarks Thereon

The most important results are shown in Tables V and VI; these include and amplify previous results (Bornstein and Lawrence, 1951), in proving that two clinical types of diabetes differ also in plasma insulin content. Table V lists 15 such cases of varying ages characterized clinically as severe, with important loss of weight and *ketonuria* as well as hyperglycaemia and glycosuria. Their blood plasma uniformly shows *no* available insulin by the above test. Thirteen other cases (Table VI), still obese and without ketosis, show considerable plasma insulin. Their mean plasma insulin is approximately 70% of the mean of 14 non-diabetic controls (Table VII), though some of the figures overlap. We consider their diabetes to be due to factors other than lack of insulin.

We found, to our surprise, that a retest of these rats four days later with previously standardized doses of insulin revealed another difference (last column of Tables V and VI). A clear diminution of retested insulin sensitivity occurred in 11 out of the 15 diabetics with no plasma insulin, but no diminution in all 13 who showed plasma insulin. Whether it is significant that three out of four in the first group were the youngest of our patients hardly merits discussion, but further investigation should certainly be made.

Tables VIII–XI show other tests that were carried out on various interesting cases, and require little explanation. It is not surprising that insulin treatment

TABLE VII.—*Normal Controls*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Plasma insulin milliunits/ml.	0.24	0.41	0.36	0.28	0.32	0.40	0.36	0.34	0.38	0.36	0.28	0.34	0.35	0.30

Mean = 0.34 milliunit/ml.

TABLE VIII.—*Patients Stabilized on Insulin. Previously no Insulin Present*

Patient	Blood Glucose at Time of Taking Blood	Plasma Insulin milliunits/ml.
29	90	0.20
30	160	0.22
31	151	0.26
32	143	0.24

TABLE IX.—*Insulin-resistant Patients. Blood Taken One Hour after 300 Units of Insulin*

Patient	Blood Glucose at Time of Taking Blood	Plasma Insulin
33	406	0
34	382	0

TABLE X.—*Acromegaly with Diabetes. Effect of Plasma on Blood Sugar of Rats*

Patient	No. of Rats	Rise in Blood Sugar with Standard Deviation
35	4	32 ± 14
36	4	88 ± 13

TABLE XI.—*Effect of Different Substances on Rats*

Dose of Insulin in milliunits	Fall in Blood Sugar Before Treatment (mg.)	Dose	Fall in Blood Sugar 4 Days After Treatment (mg.)
(a) Effect of cortisone on insulin sensitivity of ADHA rats			
0.1	23 ± 9	5 mg./rat	25 ± 7
0.2	39 ± 8	" "	37 ± 11
(b) Effect of growth hormone			
0.1	26 ± 7	1 mg./rat	24 ± 6
0.2	36 ± 9	" "	40 ± 9
(c) Effect of A.C.T.H.			
0.1	28 ± 6	10 mg./rat	24 ± 7
0.2	35 ± 8	" "	39 ± 8

restored plasma insulin to patients who previously showed none (Table VIII) and it is interesting and perhaps significant that the mean in milliunits of the insulin re-established is very similar to that in Table VI. It was also not unexpected that two insulin-resistant patients (Table IX) showed no plasma insulin one hour after a large injection—again suggesting that an inhibited factor rather than the absence of insulin is present.

Two middle-aged long-standing acromegalics with hyperglycaemia of 300–400 mg. per ml. and heavy glycosuria, but no ketosis and no previous insulin treatment, were tested. The injection of their plasma caused a rise in the blood sugar of the ADHA rats, and this is the only type of plasma which has done so.

On account of the known "diabetogenic" properties of cortisone, growth hormone, and A.C.T.H., the effect of these substances on insulin sensitivity was tested on six ADHA rats. No change was observed (Table XI) with what were judged to be adequate doses.

Finally, an attempt was made to estimate insulin in the blood of a newly discovered case of that very rare condition lipo-atrophic diabetes (Lawrence, 1951) kindly referred for the test by Professor Neale, of Bristol.

Definite evidence of plasma insulin action was obtained, but the intense lipaemia prevented a prompt separation of plasma and a satisfactory quantitative test.

The points raised by these various results tempt one to a wide discussion. But until more cases are investigated and our results are confirmed at other centres by other workers—we hope soon—we shall resist this temptation and discuss these results only briefly in relation to existing factual knowledge.

Discussion

The discovery of insulin extracted from the pancreas by Banting and Best in 1921–2 naturally led to the simple view that human diabetes resulted from deficient insulin production by the islets of the pancreas. It was easy to forget and neglect (1) that in animals eight-tenths to nine-tenths of pancreas had to be removed before diabetes resulted, and such destruction had not been shown in the usual human diabetic; and (2) that the histology of human diabetes was often near normal.

Later it appeared that other hormones, pituitary and suprarenal, could imitate a diabetic process in animals before the islets were ultimately affected. And so the simple view of primary insulin deficiency became dubious, and this doubt is supported by our results in analysing available plasma insulin.

We wish to mention and discuss some most important new work from the Toronto school on the human pancreas after death, the histological condition of the islets, (Hartroft, 1950), and the post-mortem extractable insulin of these same cases as judged by biological tests on animals: the latter paper (Wrenshall, in press) we have been privileged to read before publication by the kindness of Professor Best. They compare the pancreatic insulin content of 134 non-diabetics with 65 diabetics. Their results divide the latter into two groups: (1) diabetes which develops in the "growth-onset" period under 22 years, when practically no insulin can be extracted from the pancreas at necropsy; and (2) "maturity onset" in older patients in whom, independent of duration, the extractable insulin is about 50% of that of the normal controls. Apart from age, no clinical indications are given of weight, ketosis, etc., by which they might be related to our plasma insulin $\pm$ groups. Although their findings and ours may partially overlap in that all our young cases showed no plasma insulin, many of ours—indeed, 12 between 28 and 60 years—showed no plasma insulin. The distinction between our groups is not essentially age but loss of weight and ketosis, and really corresponds to two clinical types.

Although the results of subsequent insulin sensitivity tests after four days suggest another difference between these two types, this is not worth discussing until confirmed by many more similar results.

Conclusions

From these analyses of plasma insulin related to clinical cases we consider that two main types of human diabetes exist and can be distinguished.

The first is severe and is characterized by weight loss and *ketosis* as well as hyperglycaemia; it occurs at any age, but mainly in the young, and their plasma contains no available insulin but renders the rats insensitive to subsequent insulin injections. They require insulin treatment to live.

The second type consists mainly of middle-aged obese diabetics, females being more numerous, and is distinguished by the absence of ketosis and loss of weight. Their plasma contains available insulin, roughly 70% of normal controls, but does not make rats insensitive to insulin. Their diabetic state is easily controlled by diet alone, especially when obesity is thereby reduced.

The experiments were first carried out at the Baker Institute and the Alfred Hospital, Melbourne, and later in the Departments of Diabetes and Chemical Pathology, King's College Hospital, London, where Professor C. H. Gray deserves our best thanks. We also wish to thank Miss M. Sandiford for invaluable assistance, Dr. E. Reid for a sample of growth hormone, and Messrs. Boots Pure Drug Company for an expenses grant.

REFERENCES

- Bornstein, J. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 87, 93.
 — and Lawrence, R. D. (1951). *British Medical Journal*, **1**, 732.
 — and Trehwella, P. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 569.
 — (1951). *Med. J. Aust.*, **1**, 119.
 Hartroft, A. W. (1950). *Proc. Amer. Diabetes Ass.*, **10**, 46.
 Lawrence, R. D. (1951). *British Medical Journal*, **1**, 373.

TREATMENT OF TROPICAL ULCERS

BY

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There is already a fairly extensive literature on tropical ulcers, but the results of treatment appear to be still unsatisfactory, and towards the end of each rainy season in Tanganyika the number of ulcer cases attending hospital is embarrassing. The wide diversity of treatments recommended suggests that none is wholly satisfactory, and a study of the literature is not very helpful, as published series are often small and lack definition of the character of the ulcers treated and of criteria of cure. The results of various forms of treatment used in a series of 368 unselected in-patients treated mostly by one surgeon in two Tanganyikan hospitals may therefore be of value.

Geographical Factors and Incidence

In the present series the ulcers were all of the sloughing or phagedenic type so well described by Clements (1936), and all occurred in Africans, of whom most were employees of the Overseas Food Corporation. They were treated in two hospitals, of which one (K) is situated in Central Province on the edge of the Masai Plateau, a relatively dry scrub-land at about 4,000 feet (1,220 metres) above sea-level, with an annual rainfall of 10–15 in. (25–38 cm.). The second hospital (N) is in Southern Province, in miombo forest land at an altitude of about 1,000 feet (305 metres) and with a rainfall of 35–40 in. (89–102 cm.). In the latter region there seems to be a considerably higher incidence of yaws, bilharziasis, ankylostomiasis, and secondary anaemia than in Central Province. Nevertheless the types of ulcer seen in the two regions are essentially

similar, though involvement of bone and tendon appears to be slightly commoner and more extensive in the south. The veldt sore or desert sore type of ulcer was not found among Africans in either region.

The magnitude of the problem is illustrated by Table I, which is extracted from monthly reports by the two hospitals concerned. These do not exactly coincide with the periods covered by the present series. The relatively higher percentage of out-patient ulcer cases at hospital N compared with hospital K is probably due to the inclusion of a number of cases of secondary yaws.

TABLE I.—Incidence of Tropical Ulcers in Hospital Patients (African)

	Hospital N January 1 to December 31, 1949		Hospital K April 1, 1949, to March 31, 1950	
Out-patient department, new attendances:				
All cases	8,405		22,548	
Ulcer cases	1,141		984	
Percentage of ulcer cases	13.6		4	
	No.	Days in Hospital	No.	Days in Hospital
In-patient department, cases discharged:				
All cases	1,719	26,180	3,546	34,139
Ulcer cases	111	2,881	147	4,096
Percentage of ulcer cases	6.4	11.0	4.2	12.0

The overall average stay in hospital of the 368 cases was 26.5 days, and most patients were recommended relief from duties for about seven days after discharge, so that the expense in hospital treatment and the loss of man-power from this cause are very considerable.

Aetiology

Nutrition.—It is generally accepted that tropical ulcers occur in the under-privileged and under-nourished classes (Pattanayak, 1944; Marsh and Wilson, 1945; Rao *et al.*, 1945; Pran Nath Luthra, 1946; Triloki Nath, 1946; Blank, 1947; Adamson, 1949), and this is further confirmed in the present series as shown in

TABLE II.—Incidence of Ulcers by Occupation

Occupation	No. of Cases
Employees { Unskilled labourers	174
Semi-skilled	15
Office workers, etc.	0
Dependants of employees	6
Non-employees (local peasants)	52

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Table II. While the rations provided for labourers were adequate in calorie and vitamin content, many of the men had been undernourished for many years and had never undertaken heavy physical labour. They mostly developed ulcers before they had been long enough in the employment of the Corporation to have derived much benefit from the better food provided. In addition to their poorer physical condition, the labourers are more exposed to trauma and dirt than sedentary workers.

Circulatory Factors.—Typical phagedenic ulcers occur almost exclusively below the knee (Earle, 1942; Pattanayak, 1944; Rao *et al.*, 1945; Seshadrinathan, 1945; Pran Nath Luthra, 1946; Triloki Nath, 1946), and this is further demonstrated in Table III. What the connexion is between this regional incidence and circulatory inadequacy is not within the scope of this paper, but it should be noted that none of the cases