Brief Notes and Comments

Improvement in Both Insulin Sensitivity and Release Following Diabetic Coma

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SUMMARY

Serial estimations of both plasma insulin following intravenous glucose and the hypoglycemic potency of intravenous insulin were performed on two patients following hyperosmolar coma and in one after diabetic ketoacidosis. In all, plasma insulin and insulin sensitivity were initially low and both increased markedly over several months. Concurrently the clinical control of diabetes was possible by either oral agents or diet alone. DIABETES *20*:246-49, April, 1971.

Individuals in whom diabetic ketoacidosis has occurred will usually be permanently insulin dependent and have very low levels of circulating immunoreactive insulin (IRI).[1,2] Recently Genuth[3] reviewed this subject and described in detail two patients presenting in coma with ketoacidosis and severe infections who were subsequently both controlled without insulin. In both, plasma IRI was initially unresponsive to glucose, tolbutamide and glucagon but subsequently the responses were those of maturity onset type diabetes. The syndrome of hyperosmolar nonketotic diabetic coma is also associated with relatively low levels of plasma insulin despite the subsequent control of diabetes without insulin in the majority of survivors.[4]

The realization that glucose tolerance depends as much on the effective hypoglycemic action of insulin in an individual as on the magnitude of its release [5-7] and reports of control of diabetes without insulin despite failure of IRI to increase subsequent to ketoacidosis[8,9] led us to the investigation of insulin sensitivity in both these conditions.

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CASE REPORTS

(1). A fifty-year old, nonobese (74 kg.) man was admitted in severe diabetic ketoacidosis following a three-week history of polyuria and polydipsia. He was known to have been dia-

TABLE 1

Time after admission		Intravenous Glucose Tolerance Time										
Case 1		0	2	5	10	15	20	30	45	60	90	KGTT
7/4/67	G	196	790	380	336	308	300	280	—	272	248	0.41
(4th day)	I	4.0	4.0	4.0	4.0	4.0	4.0	4.0	—	4.0	4.0	
7/14/67	G	160	624	332	276	275	270	252	—	241	220	0.38
(14th day)	I	4.0	16	16	8	8	6	10	—	4	6	
2/18/69	G	188	364	380	364	340	308	336	—	280	260	0.46
(18 months)	I	32	33	31	29	31	27	44	—	14	12	
Case 2												
6/22/68	G	236	474	528	492	490	388	428	—	372	330	0.77
(3rd day)	I	8	5	5	7	5	6	6	—	13	5	
10/7/68	G	162	—	404	—	360	—	340	316	292	—	0.46
(4 months)	I	15	47	48	—	32	37	41	—	62	—	
Case 3												
1/26/70	G	240	504	430	446	422	442	430	400	412	—	0.20
(4th day)	I	7	5	11	9	19	19	23	—	27	—	
4/30/70	G	100	508	476	420	400	404	412	320	276	—	0.90
(3 months)	I	23	82	90	100	135	113	145	158	132	—	

G = Blood Glucose, mg. per 100 ml.; I = Plasma Insulin, μU/ml.

betic for three years but had received no treatment. On admission, his blood pressure was 140/90, and his clinical examination negative apart from 3 cm. hepatomegaly. Initial laboratory findings: blood glucose 576 mg. per 100 ml., serum sodium 123 mEq./L., potassium 4.8 mEq./L., bicarbonate 5 mEq./L., and ketones 90 mg. per 100 ml.; urine 2 per cent sugar, 1 plus albumin and strongly positive ketones; chest X ray, microurine and blood cultures negative. Good response over twenty-four hours to insulin (216 units), intravenous saline and sodium bicarbonate with urinary ketones clearing by forty-eight hours. Subsequently, 80-100 units of crystalline insulin daily required for control of diabetes for a further ten days. During this period there was no evidence of infection and he was commenced on chlorpropamide 500 mg. a day and phenformin 25 mg. t.d.s. on the tenth day with satisfactory control of the diabetes thereafter, remaining aglycosuric and free of urinary ketones. Intravenous glucose tolerance and insulin tolerance (IV_{GTT}, IV_{ITT}) were performed on the fourth and fourteenth day after admission and eighteen months later when the diabetes was well controlled on a 180 gm. carbohydrate diet and phenformin 25 mg. t.d.s., with random postprandial glucose levels 140-188 mg. per 100 ml.

(2). A fifty-four-year old man, not a known diabetic, weight 68 kg., presented in semicoma with a three-week history of intense thirst, polyuria and lassitude. On admission severely dehydrated, blood pressure 130/80, clinical examination negative apart from 4 cm. hepatomegaly. Initial blood glucose 1,360 mg. per 100 ml., serum sodium 127 mEq./L., potassium 4 mEq./L., bicarbonate 27 mEq./L., ketones 40 mg. per cent and serum osmolality 334 mOsm/kg. Urine 4 plus sugar, ketones negative and microurine negative. After treatment for twenty-four hours with intravenous saline, 214 units of insulin and 11 gm. potassium chloride (KCl), he was mentally alert with normal serum electrolytes and a blood glucose of 82 mg. per 100 ml. $IV_{GTT\text{-}ITT}$ was performed three days after admission and four months later. Tolbutamide and phenformin were administered from the tenth day after admission, but at the time of the second glucose tolerance test the diabetes was well controlled on a 150 gm. carbohydrate diet alone with random blood glucose between 71 and 168 mg. per 100 ml., the urine being free of glucose and ketones at all tests.

(3). A seventy-two-year old, nonobese (74 kg.) man, previously in excellent health, was admitted in coma, grossly dehydrated with a two-week history of severe thirst and polyuria following a virus infection. Blood pressure 110/80, clinical examination normal.

On admission his blood glucose was 1,340 mg. per 100 ml., serum sodium 130 mEq./L., potassium 5.6 mEq./L., bicarbonate 13 mEq./L., serum ketones 60 mg. per cent, blood urea 45 mg. per cent. Treatment with insulin (248 units), intravenous saline and potassium chloride (8 gm.) produced recovery in twenty-four hours despite hypotension for twelve hours. During the next fourteen days he required between 120 and 140 units of crystalline insulin to maintain blood glucose levels below 200 mg. per 100 ml. Urinary glucose and ketones were absent despite bronchopneumonia due to E. coli which responded to tetracycline. Fourteen days after admission, treatment was commenced with chlorpropamide 500 mg. a day and phenformin 25 mg. t.d.s. with good diabetic control and random blood glucose estimations between 80 and 160 mg. per 100 ml. Three months after discharge he was well controlled on a 150 gm. carbohydrate diet and chlorpropamide 250 mg. a day. $IV_{GTT\text{-}ITT}$ was performed on the fourth day and three months later and intravenous glibenclamide (2 mg.) was administered on day 19.

METHODS

Intravenous glucose tolerance tests were carried out fasting by injecting 750 mg. of glucose per kilogram body weight

TABLE 1 (Continued)

Time after admission	Intravenous Insulin Tolerance Time								
Case 1	0	5	10	15	20	30	45	60	KITT
7/4/67 (4th day)	220	228	228	220	222	208	—	200	0.40
7/14/67 (14th day)	198	184	180	172	162	150	—	120	0.98
2/18/69 (18 months)	260	244	252	236	224	200	—	144	1.16
Case 2									
6/22/68 (3rd day)	330	322	328	330	326	274	—	246	1.16
10/7/68 (4 months)	292	276	232	218	184	168	—	80	2.31
Case 3									
1/26/70 (4th day)	436	424	412	410	416	406	370	—	0.40
4/30/70 (3 months)	272	260	228	220	172	146	76	—	1.70

G = Blood Glucose, mg. per 100 ml.; I = Plasma Insulin, μU/ml.

over two minutes; sixty or ninety minutes later 0.1 units per kilogram of crystalline bovine insulin was injected intravenously and blood glucose estimated frequently for the next sixty minutes. Glucose tolerance and insulin tolerance were expressed as K_{GTT} and K_{ITT}.[6,10] The normal range in our hands is $K_{GTT} > 1.2$, K_{ITT} 2.5-11.0 mean 6.3. The validity of K_{ITT} following an overnight fast or sixty to ninety minutes after prior intravenous glucose loading was compared in eleven normal subjects. No significant difference was found between paired K_{ITT} values. Plasma IRI and growth hormone were measured by dextran charcoal[11,12] and heterologous insulin antibodies were estimated similarly by the amount I-131 insulin bound to the patient's plasma when compared to controls.[13] Blood glucose and serum ketone levels were measured routinely.[6,14]

RESULTS

The findings are shown in table 1. In each patient IV_{GTT} remained within the diabetic range. In case 1 there was an increase in basal IRI but little further rise with glucose throughout the study. However, K_{ITT} increased threefold. In cases 2 and 3, the insulin response to IV_{GTT} increased significantly over three or four months, but still exhibited a delayed rise to peak values at forty-five to sixty minutes. However, K_{ITT} increased twice and four times respectively. In case 2 fasting plasma growth hormone three days after admission was 1.0 ng./ml. and rose to 7.6 ng./ml. after hypoglycemia. In case 3, intravenous glibenclamide 2 mg. produced an insignificant rise of IRI from 17 μU/ml. to 23 μU/ml. at twenty minutes with only a modest fall in blood glucose from 100 to 70 mg. per 100 ml. at ninety minutes. In no patient was there evidence of a significant titer of insulin antibodies.

DISCUSSION

The three patients described presented acutely ill: two, cases 2 and 3, in hyperosmolar precoma and one, case 1, with diabetic ketoacidosis. In all, the subsequent clinical course was that of maturity onset, nonketotic diabetes. In cases 1 and 2 immediately following the acute illness, there was no rise in plasma insulin after intravenous glucose while in case 3 the response was low. When retested three or four months later, cases 2 and 3 showed increased plasma IRI responses to glucose with delayed rise to peak values. On retesting case 1 after eighteen months, increased basal IRI was noted with only a minimal response to glucose. Concurrently, in all three patients the hypoglycemic effect of intravenous insulin which had been initially very low, had increased two- to fourfold.

The improvement in both insulin output and sensitivity following recovery from acute illness suggests that these may be closely related, but whether insulin sensitivity directly influences insulin output or whether both are influenced by some other factor, is unknown. The possibility that both could be inhibited by epinephrine or norepinephrine exists, but none of the patients described were in shock at the time of investigation and IV_{GTT} was performed at least three days after admission when the inhibited insulin response should have returned to normal.[15,16] In nonketotic hyperosmolar coma it is possible that the level of circulating insulin is sufficient to prevent the increased lipolysis characteristic of diabetic ketosis, so permitting the gradual development of extreme hyperglycemia and dehydration with secondary beta cell failure.[17] Growth hormone does not seem to be elevated[12] and the difference between ketoacidosis may be one of degree of functional insulin insufficiency. The definite recovery of insulin release in our subjects some months after acute illness supports the hypothesis of temporary beta cell failure. In addition, our finding of a marked increase in the hypoglycemic potency of insulin suggests that insulin resistance at the time of the acute illness is a significant factor in the pathogenesis of the syndrome.

The discrepancies observed here and in other reports[18] between the clinical control of diabetes, circulating plasma IRI and glucose tolerance emphasize that in any individual the factors that determine diabetic control are at present not fully understood. Serial observations in diabetic patients and experimental animals are needed to clarify them.

ACKNOWLEDGMENT

We are grateful to Dr. C. W. Baird, Department of Biochemistry, Royal Melbourne Hospital, for the blood glucose determinations.

One of us (F.P.A.) was supported by the Sheppard Lowe Scholarship of the University of Melbourne.

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Its application to the measurement of rate of insulin disappearance. Diabetologia 6:581-85, 1970.

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ABSTRACTS

Antar, M. A.; Little, J. A.; Lucas, C.; Buckley, G. C.; and Csima, A. (Dept. of Med., Dietetics, Biochem., Epidemiology, and Biometrics, St. Michael's Hosp., Univ. of Toronto, Toronto, Ontario, Canada): INTERRELATIONSHIP BETWEEN THE KINDS OF DIETARY CARBOHYDRATE AND FAT IN HYPERLIPOPROTEINEMIC PATIENTS. 3. SYNERGISTIC EFFECT OF SUCROSE AND ANIMAL FAT ON SERUM LIPIDS. Atherosclerosis 11:191-201, March-April 1970.

Verbatim summary. Fifteen hyperlipoproteinemic patients (9 type II, 4 type III or IV, and 2 type V) were fed formula diets which simulated a typical North American diet for two, twenty-eight day periods. Total carbohydrate, fat and protein constituted 50, 35 and 15 per cent of calories respectively. The diets were high in saturated fat (P:S = 0.1) and cholesterol (310 mg./1000 calories). Substitution of 40 per cent of calories as sucrose for starch resulted in higher serum cholesterol, phospholipid and triglyceride levels in all patients. The mean increases were highly significant ($P < 0.001$, < 0.001 and < 0.01, respectively). The differences in serum lipids, especially triglyceride, were more marked for type III, IV or V than for type II patients. In view of our previous results (Parts 1 and 2 of this series) with diets high in polyunsaturated fat and low in cholesterol which showed no uniform hyperlipidemic effect for sucrose, the present findings suggest that there is a synergistic effect between dietary sucrose and animal fat. An explanatory hypothesis is discussed.

Bell, W. E.; Samaan, N. A.; and Longnecker, D. S. (Depts. of Pediat. and Neurol., University Hosp. and V. A. Hosp., Iowa City, Iowa): HYPOGLYCEMIA DUE TO ORGANIC HYPERINSULINISM IN INFANCY. Arch. Neur. 23:330-39, October 1970.

Two cases are presented with onset of hypoglycemia in infancy due to hyperinsulinism. The first child was found to have islet cell hyperplasia and remained hypoglycemic after subtotal pancreatectomy. Diazoxide restored the blood glucose to normal levels and was associated with a reduction in serum insulin content. The second case was found to be markedly leucine-sensitive and operation at age six months revealed an islet cell adenoma. Both children sustained severe brain disease secondary to persistently low blood glucose levels.

Differentiation by laboratory methods of infants with "idiopathic" hypoglycemia from those with islet cell hyperplasia or adenoma remains difficult, if not impossible. Inability to maintain an adequate blood glucose level after a brief trial of medical therapy should warrant surgery, if brain damage is to be prevented. If an adenoma is not identified, subtotal pancreatectomy should be performed. P.M.F.

Curry, Donald L.; and Curry, Katherine P. (Dept. of Physiological Sciences, Sch. of Veterinary Med., Univ. of California, Davis, Calif.): HYPOTHERMIA AND INSULIN SECRETION. Endocrinology 87:750-55, October 1970.

Isolated perfused rat pancreas was used to observe the effect of decreased body temperature on insulin secretion. A direct relationship was found between tissue temperature and the total quantity of insulin release in response to glucose or tolbutamide. By subjecting the pancreas to extreme cold and rewarming to body temperature, it was shown that partial inhibition of insulin release persists for thirty minutes after which normal secretory activity is regained. Hypothermic inhibition occurred in the presence of phentolamine, an alpha adrenergic inhibitor, excluding catecholamine suppression of insulin release as the explanation for this phenomenon. C.R.S.

Debons, Albert F.; Krimsky, Isidore; and From, Annette (Nuclear Med., Veterans Administration Hosp.; and Dept. of Surg., State Univ. of New York, Downstate Med. Center, Brooklyn, N.Y.): A DIRECT ACTION OF INSULIN ON THE HYPOTHALAMIC SATIETY CENTER. Amer. J. Physiol. 219:938-43, October 1970.

Verbatim summary. Diabetic mice, unlike normal mice, do not develop necrosis of the hypothalamic satiety center after administration of gold thioglucose. In previous studies, the rapid action of intravenously administered insulin in restoring the sensitivity of the satiety center of diabetic mice to gold thioglucose suggested that insulin might act directly on the satiety center. In the present studies, the effect of intrahypothalamic injection of insulin on the restoration of the sensitivity of the center to gold thioglucose necrosis was investigated