

PARADOXICAL HYPERGLYCEMIA FROM OVERINSULINIZATION

MARCH 27, 1969

PARKLAND MEMORIAL HOSPITAL

GRAND ROUNDS

THOUGHTS ON THE TREATMENT OF DIABETES MELLITUS

H. F. ROOT

Hypoglycemic reaction due to the administration of insulin in diabetic patients is a frequent occurrence and is, in mild form, usually harmless. It is even considered by some to be an indication of good control.

FREDERICK M. ALLEN

A superstitious fear of hypoglycemia has been widely disseminated. It is not true that well controlled patients must live under a constant danger of hypoglycemic attacks and their imagined consequences.

- - A considerable part of the bad record (development of complications or concomitants) is ascribable to careless, weak-willed or disobedient patients - -

T. S. DANOWSKI

- - the doctor - - must take but little credit for the favorable outcome and forbear punitive attitudes towards the patient -- when complications or concomitants develop.

P. H. LAVIETES AND J. P. PETERS

- - It must be recalled that overinsulinization may be followed by excessive hyperglycemia; the blood sugar must be interpreted in the light of clinical conditions lest this lead to an increase in insulin dose when reduction is in order- -

- - Attempts to insist on a normal blood sugar at any special times of day are neither practical nor necessarily desirable - -

- - Even in the best regulated cases blood sugar will, at times of the day, rise to excessive heights if, at other times hypoglycemia is to be avoided.

H. P. HIMSWORTH

I suggest that a diabetic may be considered to have achieved satisfactory physical and mental health when he has satisfied the three following standards. He must have sufficient energy for his needs; he must maintain his weight about the accepted normal figure; AND HE MUST NOT BE SUBJECT TO HYPOGLYCEMIC SYMPTOMS.

- - It is unfortunate, but it is necessary that the absence of symptoms from overdosage with insulin must be included as one of the standards of successful treatment of diabetes. TO SATISFY CHEMICAL CRITERIA AT THE PRICE OF OVERTREATMENT (HYPOGLYCEMIA) IS THE ANTITHESIS OF RATIONAL THERAPEUTICS.

J. I. GOODMAN

- - Lest the treatment become worse than the disease, avoidance of hypoglycemia is the physicians chief responsibility - -

LEO P. KRALL

- - Many diabetic patients have insulin reactions that are undetected - -
Is it because there is less awareness of insulin reactions; have the symptoms changed or are the symptoms so mild that they are hard to recognize and thus of little importance?

- - All these questions may be answered "yes" except that all insulin reactions must be considered important.

AIMS IN TREATMENT OF DIABETES

I. Immediate Goals

- (1) Prevention of ketoacidosis
- (2) Prevention of obligatory polyuria (osmotic diuresis)
- (3) Prevention of hypoglycemia
- (4) Normalization of the blood glucose - but never buy "chemical control" at the price of hypoglycemic episodes

II. Distant Goals

- (1) Prevention of the complications or amelioration of the genetic concomitants of the diabetic state i.e. micro-angiopathy (retinopathy, K-W, neuropathy, gangrene)
- (2) Prevention of accelerated atherosclerosis

DANGERS OF HYPOGLYCEMIA

1. Permanent cerebral damage
2. Death of patient
3. Death of others - auto accidents, etc.
4. Precipitation of angina, myocardial infarction or arrhythmia
5. Worsening of the diabetic state
 - a. Precipitation of paradoxical hyperglycemia
 - b. Precipitation of ketoacidosis

Case 1 - J.K. - This 56 year old man with diabetes of 3 years duration had been followed in Diabetes Clinic since onset of his diabetes and was well controlled on 40 u of NPH insulin a day. The head nurse in the Diabetes Clinic called attention to the patient because she was suspicious that he was obtaining insulin for non-clinic patients. Apparently he had been returning to clinic at frequent intervals for refill of his prescription. When seen by a physician it was discovered that he was using a 5 cc syringe instead of a 1 cc insulin syringe. He had broken his syringe while visiting his daughter in a nearby city. She gave him the 5 cc syringe that was left in her home years before by a visiting physician. Instead of taking 50 u a day the patient had been taking 200 u a day. A 16 lb. weight gain was documented over the past month. He had no symptoms of hypoglycemia except for excessive driven hunger and occasional nervousness and tremulousness relieved by eating.

Case 2 - L.C.S. - This 37 year old woman from Waco, Texas with known diabetes of 2 years duration was referred to PMH because of worsening of her diabetes over a 6 month period. During this time her insulin requirements increased progressively from 50 u to 110 u of NPH insulin per day. When previously well controlled her FBS ranged between 90-120 mg%. In the past 6 months excessive glycosuria was associated with increasing hyperglycemia. During the past month FBS were in the range of 100-340 mg%. Careful history disclosed that the patient suffered from occasional nightmares and frequent mid-morning headaches relieved by eating lunch. In addition her family noted marked personality changes in the late afternoon characterized by temper tantrums, aggressive and at times belligerent behavior. According to her daughter this improved markedly following the evening meal. The patient responded promptly to alteration in the distribution of calories in her diet and reduction in insulin. Within 1 week insulin was reduced to 35 u a day which produced FBS in the range of 130-150.

PHYSIOLOGIC ACTIONS OF INSULIN

- | | |
|---------|--|
| LIVER | <ol style="list-style-type: none">1. Decreases Hepatic Glucose Output by Decreasing Glycogenolysis and Gluconeogenesis2. Converts the Liver from an Organ of Glucose Output to One of Glucose Uptake3. Increases Glycogen Synthesis4. Decreases Ketogenesis |
| MUSCLE | <ol style="list-style-type: none">1. Increases Glucose Utilization2. Decreases Amino Acid Outflow3. Increases Protein Synthesis |
| ADIPOSE | <ol style="list-style-type: none">1. Increases Glucose Utilization2. Increases Lipogenesis3. Decreases Lipolysis - reduces outflow of FFA to Liver and MM |

SYMPTOMS AND SIGNS OF HYPOGLYCEMIA

I. SYMPATHETIC DISCHARGE - HYPEREPINEPHRINEMIA

Restlessness	Sweating
Anxiety	Tachycardia
Palpitations	Tremulousness

II. CNS - INADEQUATE CEREBRAL DELIVERY OF GLUCOSE

Mental Disturbances - Personality Changes

Slow cerebration	Bizarre behavior
Irritability	Disorders of speech
Aggressiveness	Disorders of gait
Negativism	Headaches - Nightmares

Somnolent - Agitated States

Tumbling, writhing, eylling, monoplegias,
Hemiplegias, blindness
Incoorination of eye muscles
Positive Babinski

Deep Coma

Flaccidity or	Trismus
Decerebrate rigidity	Extensor rigidity
Hypothermia	convulsions

HYPOGLYCEMIA - GENERAL REVIEWS

1. Conn and Seltzer, H. Spontaneous hypoglycemia. Am. J. Med. 19:460, 1955.
2. Freinkel, N. and Bleicher, S. J. The physiologic basis for evaluation of "Fasting Hypoglycemias". Am. J. Surg. 105:730, 1963.
3. Yalow, R. S. and Berson, S. A. Dynamics of insulin secretion in hypoglycemia. Diabetes 14:341, 1965.
4. Arky, R. Hypoglycemia. Disease-A-Month, Feb. 1968.

PARADOXICAL HYPERGLYCEMIA AND OVERINSULINIZATION

5. Mintz, D. H., et al. Hormonal genesis of glucose intolerance following hypoglycemia. Am. J. Med. 45:187, 1968.
6. Somogyi, M. Exacerbation of diabetes by excess insulin action. Am. J. Med. 26:169, 1959.
7. Somogyi, M. Diabetogenic effects of hyperinsulinism. Am. J. Med. 26:192, 1959

8. Perkoff, G. T. and Tyler, F. H. Paradoxical hyperglycemia in diabetic patients treated with insulin. Metabolism 3:1010, 1954.
9. Somogyi, M. and Goldwasser, H. V. Quantitative relationship between insulin dosage and amount of carbohydrates utilized in diabetic persons. Am. J. Med. 26:165, 1959.

THOUGHTS ON THE PRINCIPLES OF DIABETIC TREATMENT

10. Allen, F. M. A personal view of therapy of diabetes. Diabetes 11:336, 1962.
11. Danowski, T. S. Some principles of diabetic care. Diabetes 9:292, 1960.
12. Laviates, P. H. and Peters, J. P. The treatment of diabetes. New Internat. Clinics 2:170, 1941.
13. Himsworth, H. P. Protamine insulin and PZI in the treatment of diabetes mellitus. Brit. Med. J. 1:541, 1937.
14. Goodman, J. I. Causes of labile diabetes: Its treatment. Am. J. Med. 18:448, 1955.
15. Aring, C. D. Diabetic neuritis. AMA Archives of Neurology 2:211, 1960.

HYPOGLYCEMIC REACTIONS - CLINICAL PICTURES AND PATHOPHYSIOLOGY

16. Maddock, R. K. and Krall, L. P. Insulin Reactions - Manifestations and need for recognition of long-acting insulin reactions. AMA Arch. Int. Med. 91:695, 1953.
17. Balodimos, M. C. and Root, H. F. Hypoglycemic insulin reactions without warning symptoms. J.A.M.A. 171:261, 1959.
18. Madison, L. L. Ethanol-induced hypoglycemia - Signs and symptoms of hypoglycemia in Advances in Metabolic Disorders 3:89, 1968. Luft and Levine, eds.

CEREBRAL GLUCOSE METABOLISM

19. Fazekas and Bessman. Coma mechanisms. Am. J. Med. 15:804, 1953.
20. Rowe, et al. A study in man of cerebral blood flow and cerebral metabolism of glucose, lactate and pyruvate metabolism before and after eating. J. Clin. Invest. 38:2154, 1959.
21. Hamrick, L. W. Jr. Catheterization of the internal carotid artery for the study of cerebral metabolism with observations on insulin. (Abst) South. Soc. Clin. Res. 1954, pg. 4.

22. Eisenberg, S. and Seltzer, H. The cerebral metabolic effects of acutely induced hypoglycemia in human subjects. *Metabolism* 11:1162, 1962.
23. Reinmuth and Scheinberg and Bournon. Total cerebral blood flow and metabolism. *Arch. Neur.* 12:49, 1965.
24. Butterfield, et al. Insulin sensitivity of the human brain. *Lancet*, May 12, 1966, pg. 557.

COUNTER-REGULATORY RESPONSES TO HYPOGLYCEMIA

EPINEPHRINE

25. Amatuzio, D. S. et al. The effect of epinephrine, insulin, and hyperthyroidism on the rapid I.V. glucose tolerance test. *J. Clin. Invest.* 33:97, 1954.
26. Goldfein, A. et al. Plasma epinephrine and norepinephrine levels during insulin-induced hypoglycemia in man. *J. Clin. Endo. & Metab.* 21:296, 1961.
27. Hokfelt, B. and Bydeman, S. Increased adrenalin production following administration of 2-Deoxy-D-glucose in the rat. *Proc. Soc. Exp. Biol. and Med.* 106:537, 1961.
28. Luft, R., Cerasi, E., Madison, L. L., Von Euler, U.S., Della Casa, L. and Roovette, A. Effect of small decrease in blood-glucose on plasma growth hormone and urinary excretion of catecholamine in man. *Lancet* 2:254, 1966.
29. Fritz, I. B., et al. Effects of epinephrine and insulin on glucose disappearance in eviscerated dogs. *Am.J. Physiol.* 189:57, 1957.
30. Butcher, R. W. Role of cyclic AMP in hormone action. *N.E.J.M.* 279:1378, 1968.
31. Porte, D. Jr. et al. The effect of epinephrine on immunoreactive insulin levels in man. *J. Clin. Invest.* 45:228, 1966.
32. Porte, D. Jr. A receptor mechanism for the inhibition of insulin release by epinephrine in man. *J. Clin. Invest.* 46:86, 1967.
33. Sokal, J. E. et al. Relative potency of glucagon and epinephrine as hepatic glycogenolytic agents: studies with isolated perfused rat liver. *Endoc.* 74:930, 1964.
34. Ezdinli, E. Z. and Sokal, J. E. Comparison of glycagon and epinephrine effects in the dog. *Endocrinology* 78:47, 1966.
35. Sarcione, E. J., Sokal, J. E. and Gerszi, K. I. Relationship of the adrenal medulla to the hyperglycemic effect of glucagon. *Endocrin.* 67:337, 1960.

36. Sarcione, E. J. et al. Elevation of plasma epinephrine levels produced by glucagon in vivo. *Endocr.* 72:523, 1963.
37. Lawrence, A. M. and Forland, M.: Glucagon provocative test for pheochromocytoma. *J. Lab. & Clin. Med.* p. 878, 1964.

GLUCAGON

38. Ohenda, A. and Unger, et al. Control of pancreatic glucagon secretion by glucose. *Diabetes* 18:1, 1969.
39. Buchanan, et al. Effect of blood glucose on glucagon secretion in anesthetized dogs. *Diabetes* 18:11, 1969.
40. Ketterer and Unger. The effect upon insulin secretion of physiologic doses of glucagon administered via the portal vein. *Diabetes* 16:283, 1967.
41. Sokal, J. E. Glucagon-an essential hormone. *Am. J. Med.* 41:331, 1966.
42. Exton and Park. Control of gluconeogenesis in liver. II. Effects of glucagon, catecholamines and 3'5' AMP on gluconeogenesis in the perfused rat liver. *J. Biol. Chem.* 243:4189, 1968.
43. Lefebvre, P. Present hypothesis concerning the physiologic role of glucagon. *Acta Diabetologica Latina* 5:143, 1968.
44. Samols, et al. Promotion of insulin secretion by glucagon. *Lancet* 2:415, 1965.

GROWTH HORMONE

45. Glick, Roth, Yalow and Berson. The regulation of growth hormone secretion. *Rec. Prog. in Hormone Res.* 21:241, 1965.
46. Levine and Luft. The relation between the growth and diabetogenic effects of the so-called growth hormone of the anterior pituitary. *Diabetes* 13:651, 1964.
47. Rabinowitz, et al. Growth hormone-insulin interaction - Fact and Speculation. *Diabetes* 15:905, 1966.
48. Ikkos, Luft and Gemzell. Effect of human growth hormone in man. *Acta Endocrin.* 32:341, 1959.
49. Luft, Cerasi, Madison, von Euler, Della Casa and Roovette. Effect of a small decrease in blood glucose on plasma-growth-hormone and urinary excretion of catecholamines in man. *Lancet* July 30, 1966 - pg 254.

50. Madison, Luft and Seyffert. Acute effect of physiologic and pharmacologic doses of growth hormone on hepatic glucose output and peripheral glucose utilization. Protein & Polypeptide Hormones, Excerpta Medica Foundation, Pt. 2, pg 529, 1968.

CORTISOL

51. Weber, et al. Action of glucocorticoid as inducer and insulin as suppressor of biosynthesis of hepatic gluconeogenic enzymes. Advan. Enzym. Regulat. 3:43, 1965.
52. Ashmore, J. The effects of glucocorticoids on insulin action. Diabetes 13:349, 1964.
53. Exton and Park. Control of gluconeogenesis in the perfused liver of normal and adrenalectomized rats. J. Biol. Chem. 240:955, 1965.
54. Lecocq, Mebane and Madison. The acute effect of hydrocortisone on hepatic glucose output and peripheral glucose utilization. J. Clin. Invest. 43:237, 1964.
55. Engel and Scott. The insulin-glucose tolerance test. A modified procedure for detection of hypoglycemic unresponsiveness in pituitary and adrenal insufficiency. J. Clin. Invest. 29:151, 1950.
56. Greenwood, et al. Plasma sugar, FFA, cortisol and growth hormone response to insulin. J. Clin. Invest. 45:429, 1966.

FREE FATTY ACIDS, KETONES AND KETOSIS

57. Abramson, E. A. and Arky, R. A. Role of beta-adrenergic receptors in counterregulation to insulin-induced hypoglycemia. Diabetes 17:141, 1968.
58. Goodner, C. J. et al. Studies of substrate regulation in fasting. I. Evidence for central regulation of lipolysis by plasma glucose mediated by the sympathetic nervous system. Diabetes 16:576, 1967.
59. Werk, E. E. Jr. et al. Effect of sympathetic blockage on changes in blood ketones and nonesterified fatty acids following hypoglycemia in man. Metabolism 10:115, 1961.
60. Havel, R. J. and Goldfien, A. The role of the sympathetic nervous system in the metabolism of FFA. Jour. Lipid Res. 1:102, 1959.
61. Goldfein, A. et al. Evidence for centers in the CNS that regulate fat mobilization in dogs. J. Lipid Res. 7:357, 1966.
62. Seyffert, W. A. and Madison, L. L. Physiologic effects of elevation of plasma FFA on hepatic glucose output, peripheral glucose utilization, serum insulin and plasma glucagon. Diabetes 16:765, 1967.

63. Madison, et al. The hypoglycemic action of ketones: Evidence for a stimulatory feedback of ketones on the pancreatic beta cells. J. Clin. Invest. 43:408, 1964.
64. Engel, F. L. and Amatruda, T. T. Hormonal aspects of ketosis. Ann. N. Y. Acad. Sci. 104:753, 1964.
65. Houssay, B. A. Hormonal factors of diabetic ketosis. Diabetes 12:481, 1963.
66. McPherson et al. Studies on ketone metabolism in man. The effect of glucose, insulin, cortisone, and hypoglycemia on splanchnic ketone production. J. Clin. Invest. 47:1379, 1958.
67. Penick et al. Fall in plasma FFA associated with the sight of food. N.E.J.M. 275:416, 1966.