MEDICAL GRAND ROUNDS February 13, 1975

INSULINOMA

Case 1 [redacted]

This 67 year old woman was admitted to [redacted] for the 5th time on [redacted]-74 and died 40 days later. Her history is extremely complicated. A brief chronological review is as follows. At age 27, and again at age 35 she described several hour periods of paresthesias over the left side of the body which subsided spontaneously. In 1962, at age 55 she developed similar symptoms on the right side and in 1964 had a transient left hemiplegia. She was first admitted to [redacted] in 1967 complaining of dizziness and blurred vision. She was found to have extensive arteriosclerosis and by angiography was shown to have 100% occlusion of the right external carotid, 20% occlusion of the right subclavian, 50% occlusion of the left internal carotid, 50% occlusion of the right renal and 60% occlusion of the left common iliac arteries. On [redacted] 1967 she had an uneventful right carotid endarterectomy. Symptomatic response was good and her dizziness and paresthesias disappeared. During this hospitalization she was found to have hypertension (with diastolic blood pressures up to 110 mm mercury) and hypercholesterolemia in the range of 300-380 mgs%. Triglyceride concentrations in the fasted state were around 250 mgs%. Her hypertension was treated with thiazide diuretics and methyldopa, while therapy for hypercholesterolemia consisted of a polyunsaturated fat diet and bile salt binding resins (cholestyramine and subsequently colestipol). In general response to treatment of both conditions was satisfactory with blood pressures averaging 140/90 and cholesterol ranging from 230-275 mgs%.

She was next admitted in 1970 with severe exacerbation of trigeminal neuralgia which had first appeared in 1959. The pain subsided spontaneously, but subsequently returned, requiring re-admission to the hospital. In [redacted] of 1970 she underwent a right temporal craniotomy with section of the 5th nerve.

In 1973 the patient began to have severe angina pectoris and in [redacted] of that year was admitted with a 10 day history of worsening chest pain. Electrocardiograms were highly suggestive of subendocardial myocardial infarction although no serum enzyme changes were noted. No evidence for congestive heart failure was obtained.

She did well until approximately three days prior to the final admission when her husband was awakened during the night because of the patient's noisy breathing. He found her to be "icy-cold" and unable to answer questions. A glassy stare was noted. She was brought to the Parkland emergency room where a diagnosis of transient cerebral ischemia was made on the basis of previous history. After about 4 hours, during which she was described as being confused and lethargic, she suddenly became alert and lucid without treatment,

although she was amnesic for the episode. She was discharged to be followed in clinic. She did well for two days, but on the day of admission was found early in the morning sitting in the bathtub without water. She refused to leave the tub and was once again described as being cold to the touch. She was brought again to the emergency room where it was found that her blood sugar was 39 mg%. She was then admitted to the hospital.

There was no history of syncope, convulsions, weight gain or weight loss. There was no family history of ulcer disease, diabetes, or other endocrinopathies. She had never taken insulin or hypoglycemic drugs except for propanolol which had been prescribed for angina. She did not drink alcohol and had no history of liver disease. She had been menopausal for 28 years. No increase in skin pigmentation had been noted.

On admission (following glucose), B.P. was 140/80, pulse 86, respirations 14 and temperature 96° rectally. She was oriented but lethargic. No xanthomas were noted in the skin. Pupils were round, regular, and equal, responsive to light, and fundoscopic exam was normal. Ears, nose and throat were free of abnormalities. The thyroid was not felt. The carotids were palpable but a bruit was heard on the right. The lungs were clear and the heart was not enlarged. The rhythm was regular and there was no murmurs. Abdominal exam was negative with no organs or masses palpable. The genitalia were normal internally and externally. Bilateral varicose veins were noted in the legs, but no edema or muscle weakness was present. She was able to walk without difficulty. No pulses were palpable on the left, but the femoral and dorsalis pedis arteries were felt on the right. Cranial nerves were intact and stretch reflexes were normal. No pathological reflexes were noted.

Apart from hypoglycemia, the initial laboratory workup was normal. Skull series showed the results of the previous craniotomy and EEG showed a right sided focus, presumably also a post-surgical defect. Brain scan was normal. Plasma cortisol was 24 µG% and T_4 was 8.8 µG%. Liver function studies were normal except for an SGOT of 96. Liver-spleen scan was normal. Despite the fact that the patient was eating and receiving intermittent intravenous glucose, plasma concentrations remained low. The initial paired glucose and insulin values were as follows:

Date	Time	Plasma glucose mg%	Plasma Insulin µU/ml	I/G ratio
[redacted]-74	1900	106	168	1.6
[redacted]-74	0100	51	153	3.0
[redacted]-74	0700	28	145	5.2
[redacted]-74	0200	35	158	4.5
[redacted]-74	0700	33	133	4.0
[redacted]-74	0700	<25	108	>4.3

For the remainder of the patient's hospitalization massive amounts of intravenous glucose were required to maintain the blood sugar above 100 mg%. An average of 35-45 G per hour was given as a 25% solution. On [redacted]-74 celiac

and mesenteric arteriograms were performed and showed a 1.8 cm tumor in the head of the pancreas. During the arteriograms and again on [redacted]-74 the patient complained of pressing chest pain, relieved by nitroglycerine. Electrocardiograms showed inverted T waves and depressed ST segments suggestive of subendocardial infarction. A myocardial scan was positive for infarction on [redacted]-74 and she was transferred to the coronary care unit.

During her hospital course a variety of medical interventions were tried, including propranolol, IV diazoxide up to 1200 mg per day and dietary supplementation with medium chain triglycerides. None of these maneuvers decreased the glucose requirements. On [redacted]-74, after careful explanation of the risks to patient and family, exploratory laparotomy was carried out. An islet cell carcinoma was found in the head of the pancreas. The tumor could not be completely removed. The patient did well for 24 hours following surgery with blood sugars in the 200-400 mgs% range and much less glucose was required. Three days post-op she became febrile and subsequently developed renal shut down unresponsive to fluid therapy. On [redacted]-74 she developed a right hemiparesis, began to have bloody stools and on [redacted]-74 experienced a cardiac arrest. Permission for postmortem exam was denied.

A sample of her plasma was obtained pre-operatively and was sent to Dr. Arthur H. Rubenstein of the University of Chicago. Total immunoreactive insulin was 54 μU/ml. On column fractionation, 88% was found to be proinsulin (47.4 μU/ml).

Case 2 [redacted]

This 63 year old man developed symptomatic diabetes mellitus in [redacted], 1972. He was treated initially with tolbutamide and phenformin but obtained no response, blood sugars running around the 450 mg% mark. In [redacted] of 1972 he was switched to insulin, but hyperglycemia persisted. In [redacted] 1972 he was admitted to [redacted] for control of diabetes. Large amounts of insulin were required and there was no evidence that a Somogyi phenomenon was operative. At discharge he was taking 120 units of NPH insulin in the morning and 40 units in the evening. He was readmitted in [redacted], 1973 when he was found to have multiple tooth abcesses and a series of extractions were carried out. Insulin requirements appeared to decrease and he was discharged on 50 units of NPH insulin and restarted on tolbutamide and phenformin. The rationale for this rather unusual therapy was apparently that removal of the chronic sites of infection would restore insulin sensitivity. It became evident that this was not so and the patient reverted to a pattern of severe hyperglycemia and polyuria. It is of interest that a plasma sample was obtained for insulin antibodies during the previous admission and was subsequently reported to be very high. In view of the insulin resistance prednisone therapy was started in [redacted] 1973. A dose of 60 mg per day was ordered, but the patient reportedly took only 15 mg daily. When seen in the clinic fasting plasma glucose values over the next few months ranged from 315 to 396 mgs% as insulin dosage was gradually

increased. In [redacted] of 1973, while taking 80 units of NPH insulin in the morning and 65 units in the evening the fasting glucose was 186 mgs. Prednisone was then gradually decreased until [redacted]-74, when it was stopped. A summary of his clinical course during this time was as follows:

Date	Wt	FBS (mg%)	Insulin (total units)	Prednisone (mg)
[redacted]-73	132	365	90	15
[redacted]-73	133	330	115	15
[redacted]-73	141	396	130	15
[redacted]73	146	351	140	15 qod
[redacted]-73	158	186	145	10 qod
[redacted]-73	150	190	145	5 qod
[redacted]-73	--	170	145	5 qod
[redacted]-74	176	177	145	2.5 qod
[redacted]-74	181	72	140	D.C.

On [redacted]-74 the patient "blacked out" and was brought to the emergency room where he responded rapidly to IV glucose. Insulin dosage was decreased and he was sent home. On [redacted]74 a similar episode occurred. By the time of arrival the blood sugar was 87 mgs%, but again the patient responded symptomatically to IV glucose. He was then admitted to the hospital for workup. The patient's history is made more complicated by the discovery in 1972 that he had hyperglobulinemia. Marked elevations of IgA, IgM, and IgG were noted and kappa and lambda light chains were found in the urine. The bone marrow showed 10% plasma cells and x-rays of the scapula and humerus showed lesions which were suggestive of multiple myeloma.

Additional problems included a trunkal ataxia of uncertain etiology, present for 1 year, and an axillary vein thrombosis which occurred in [redacted] 1973. Finally he had been treated on two occasions for a positive spinal fluid serology.

Physical examination on admission showed a B.P. of 120/80, pulse of 84, respiration of 12 and temperature of 98^{8}. The head was normal. Pupils were regular and equal and reacted to light and accommodation. No nystagmus was noted. He had bilateral cataracts and the retinas were not well visualized. The nasal septum was not perforated. Ears, nose and throat were normal. The thyroid was not palpable, but anterior cervical nodes were felt bilaterally. The lungs were clear and the heart was normal except for an apical systolic murmur, grade 2. The liver and spleen were not palpable and no masses were felt. The genitalia and rectum were normal; the prostate was not enlarged. The extremities showed no clubbing, cyanosis or edema. Neurological revealed an unsteady gait with a questionable Romberg. Cranial nerves were intact and motor strength was good. He had a decreased vibratory perception in the right leg but sensory patterns were otherwise intact. Reflexes were normal.

On the first hospital day insulin was decreased to 80 units, but at 0400 the following morning the blood sugar was 40 mgs%. Insulin was decreased

to 60 units on the second day and hypoglycemia once again supervened (at 1530) with loss of consciousness and subsequent transient left hemiplegia. At this point all insulin was stopped. Despite the absence of insulin and intake of a regular diet supplemented by IV glucose, the patient had blood sugars on many occasions in the 30-40 mgs% range.

An extensive workup was carried out in the hospital. He had no evidence of renal failure. Endocrine evaluation ruled out the possibility of pituitary or adrenal insufficiency. T_4 was 7.9 µG%. Plasma cortisol ranged from 8-27 µG% and urinary 17-OH steroids were 10.1 mg/24 hrs basal and 19 mg/24 hr after metapyrone. The values on the ACTH test were 10.6 mg basal and 27 mg after corticotropin infusion. Plasma ACTH by immunoassay was 132 pg/ml, a high value. Plasma glucagon during a hypoglycemic episode (25 mg%) was 165 pg/ml while free plasma insulin determined in Dr. Unger's laboratory 38 µU/ml. On [redacted]-74, when the blood sugar was 72 mgs% the free plasma insulin determined in the laboratory of Dr. Arthur H. Rubenstein at the University of Chicago was 50 µU/ml with a total insulin (antibody bound plus free) of 3346 µU/ml. The C-peptide activity was very high, 14.3 ngs/ml, indicating marked endogenous insulin secretion.

Mr. [redacted] continued to have a high sedimentation rate and elevated serum globulins, which by immunoelectrophoresis proved to be a panhypergammaglobulinemia in Dr. Stone's laboratory. There was a moderate increase in IgA and IgD, a mild increase in IgG and IgM and no increase in IgE. In addition there was multiple component proteinuria consisting of albumin and kappa and lambda light chains. Bone marrow was not diagnostic of multiple myeloma.

On [redacted]-74, against medical advice, the patient left the hospital. He has since been seen regularly in the clinic and is asymptomatic on no treatment. His course follows:

Date	Wt	FBS
[redacted]-74	166	70
[redacted]-74	162 1/2	69
[redacted]-74	163	81
[redacted]-74	172	78
[redacted]-74	178	80

Repeat evaluation of his plasma by Dr. Rubenstein on [redacted]-74 showed:

C peptide - 7.0 ng/ml
Free insulin - 60.6 µU/ml
Total insulin- 1669 µU/ml

The plasma glucose, obtained simultaneously, was 69 mg%.

Interestingly, muscle capillary basement membrane thickness, determined by Dr. Philip Raskin, was 2713 Å. This is a markedly elevated value and is compatible with the diagnosis of genetic diabetes mellitus.

COMMENTS AND SELECTED BIBLIOGRAPHY

In considering islet cell tumors two relatively recent reviews are of prime interest. They are quite comprehensive regarding the clinical history and current concepts of treatment for insulinomas, but are deficient in details about clinical testing.

1. Schein, P. S., R. A. DeLellis, C. R. Kahn, P. Gordon and A. R. Kraft. Islet cell tumors:current concepts and management. Ann. Int. Med. 79:239-257, 1973.
2. Stefanini, P., M. Carboni, N. Patrassi and A. Basoli. Beta-islet cell tumors of the pancreas:results of a study on 1067 cases. Surgery 75:597-609, 1974.

Islet cell tumors are relatively rare, but their true incidence is hard to ascertain. Stefanini and co-workers (2) were able to find 1067 cases by reviewing the medical literature and contacting authors who had written about the disease to get their unpublished patients. Shatney and Grage (3) were able to identify 67 islet neoplasms in Minneapolis-St. Paul between 1934 and 1974, 27 of which were functioning insulinomas. Kovlie and White (4) found 21 cases in the records of 14 Seattle hospitals between 1950 and 1970. These hospitals were estimated to admit 80% of the patients in greater Seattle which at the time had a population of 1,250,000 people. The incidence of islet cell tumors at autopsy has been given as .08% (3). An educated guess would be that 1-5 cases per year should be seen in Dallas each year. While the incidence of insulinomas is low, the diagnosis of hypoglycemia is common. It therefore becomes necessary to rule the diagnosis in or out very much more frequently than would be predicted from the number of confirmed tumors in the population.

3. Shatney, C. H. and T. B. Grage. Diagnostic and surgical aspects of insulinoma. A review of twenty-seven cases. Amer. J. Surg. 127:174-184, 1974.
4. Kovlie, H. and T. T. White. Pancreatic islet beta cell tumors and hyperplasia:experience in 14 Seattle hospitals. Ann. Surg. 175:326-335, 1972.

Clinical diagnosis

It is a remarkable fact that many patients with proven insulinoma are undiagnosed for prolonged periods of time; i.e., hypoglycemia was not suspected despite the symptoms. The two most common mis-diagnoses are epilepsy (because of repeated hypoglycemic convulsions) and neuropsychiatric syndromes. Fujji and co-workers, reporting on 9 cases of documented insulinoma, point out that a period of 4 years elapsed before the diagnosis was made in 5 of the patients (5). The extensive review of Stefanini, et al (2) revealed the following (Table I):

5. Fujji, K., S. Yamogata, R. Sasaki, A. Ohneda, T. Shoji and J. Suzuki. Arteriography in insulinoma. Amer. J. Roent. Rad. Ther. Nuc. Med. 120:634-647, 1974.

Table I

Time to diagnosis	% of patients
< 1 year	34
1-5 years	46
> 5 years	20

The reason for this difficulty is that insulin secreting tumors only rarely present with the typical epinephrine-induced symptoms of nervousness, sweating and tachycardia that characterize the rapid falls in plasma glucose seen in hypoglycemia due to exogenous insulin therapy (the most common form of hypoglycemia). This is presumably due to the fact that the fall in blood glucose is generally slow enough to avoid activation of hormonal counter-regulatory responses. The breakdown of symptoms in 1067 patients was as follows:

Table II (ref 2)

Symptomatology in insulinoma	Percent of patients
CNS(coma,dizziness,convulsions,abnormal behavior)	92
Irreversible CNS damage (stroke)	7
Temporary paralysis	5
Cardiovascular symptoms(palpitation,precordial pain, etc.)	17
Gastrointestinal symptoms (hunger,nausea and vomiting)	9

Baruh, et al (6) also emphasize that CNS symptoms predominate in insulinoma. Our patient, Mrs. [redacted], illustrates the problem. While her diagnosis was made relatively early, the correct diagnosis was not made on her first visit to the emergency room because she had another obvious cause for her symptoms. In this regard the advice of Seltzer (7) seems well taken. Reviewing the problem of drug-induced hypoglycemia, he states: "Drug-induced hypoglycemia is now so relatively common that virtually every unconscious patient should be considered hypoglycemic until immediate estimation of the blood sugar level rules the condition in or out." This philosophy should be expanded to include all abrupt behavioral changes even if consciousness is not impaired. It must also be recognized that blood sugar may have rebounded into normal levels if time between onset and arrival at the hospital is prolonged. CNS symptoms may persist after the blood sugar has been restored to normal by counter-regulatory mechanisms, particularly if the level of hypoglycemia was extreme or vascular disease of the brain is present.

6. Baruh, S., L. Sherman, H. D. Kolodny and A. J. Singh. Fasting hypoglycemia. Med. Clin. N. Amer. 57:1441-1462, 1973.
7. Seltzer, H. S. Drug-induced hypoglycemia. A review based on 473 cases. Diabetes 21:955-966, 1972.

An additional clue to the diagnosis of hypoglycemia, is the presence of hypothermia (8). This was true in the protocol case. It is of great interest that diminished body temperature may persist for up to 6 hours after an hypoglycemic episode.

8. Freinkel, N., B. E. Metzger, E. Harris, S. Robinson and M. Mager. The hypothermia of hypoglycemia. Studies with 2-deoxy-D-glucose in normal human subjects and mice. N. Eng. J. Med. 287:841-845, 1972.

Differential diagnosis of hypoglycemia

The differential diagnosis of hypoglycemia, once it is recognized, is complicated. The hallmark of hyperinsulinism is fasting hypoglycemia. As far as can be told there is only one case report of an islet cell tumor in which symptoms never occurred with fasting but appeared only after a carbohydrate challenge (9). This remarkable patient convulsed after the administration of intravenous glucose, demonstrating plasma insulin values of up to 12,900 μU/ml 5-10 minutes after glucose injection.

9. Power, L. A glucose-responsive insulinoma. J.A.M.A. 207:893-896, 1969.

However, there are many other conditions which cause fasting hypoglycemia. The major causes are listed in Table III.

10. Ensinck, J. W. and R. H. Williams. Disorders causing hypoglycemia in R. H. Williams, Editor, Textbook of Endocrinology, W. B. Saunders Company, Philadelphia, 1974. pp 627-659.
11. Fajans, S. S. Hyperinsulinism, hypoglycemia and glucagon secretion in M. M. Wintrobe, G. W. Thorn, R. D. Adams, E. Braunwald, K. J. Isselbacher and R. G. Petersdorf, Editors, Harrison's Principles of Internal Medicine, McGraw-Hill, New York, 1974. pp 554-561.

It should be understood that the categorization of hypoglycemia into underproduction and overutilization syndromes represents a generalization within which overlap occurs. For example, in severe malnutrition the underproduction of glucose that results from depletion of gluconeogenic substrate (amino acids, glycerol) may also be accompanied by overutilization of glucose since depletion of body fat stores lowers plasma free fatty acid levels. As a consequence those tissues which ordinarily utilize free fatty acids (muscle, heart, kidney, gut) or their derivative substrate, the ketone bodies (central nervous system), became absolutely dependent on glucose resulting in enormous rates of utilization of the latter. Similarly, while hyperinsulinism causes glucose overutilization it is highly likely that hepatic glucose production is also dampened (12). Nevertheless, from a clinical viewpoint, the classification is often

Table III

Causes of fasting hypoglycemia

Conditions primarily associated with the underproduction of glucose	
a. Hormone deficiencies	b. Enzyme defects
Hypopituitarism	Glucose-6-phosphatase (Von Gierke)
Addison's disease	Liver phosphorylase (Hers)
Adrenal medullary insufficiency	Branching and debranching enzymes
Glucagon deficiency	Fructose-1, 6-diphosphatase
c. Substrate deficiency	d. Acquired liver disease
Severe inanition	Hepatic congestion
Ketotic hypoglycemia of infancy	Cirrhosis
	Severe hepatitis
e. Drugs	
Ethanol	
Others	
Conditions associated primarily with over-utilization of glucose	
a. Hyperinsulinism	b. Extrapancreatic tumors
Insulinoma	
Exogenous insulin	
Sulfonylureas	

helpful. If one can demonstrate glucose overutilization and if one is not dealing with end-stage starvation, then it can be assumed that the cause of hypoglycemia is either hyperinsulinism or an extrapancreatic tumor. In general if more than 200 G of intravenous glucose is required to maintain the patient in a euglycemic state it can be assumed that overutilization is present. This follows from the fact that hepatic glucose production after early fasting occurs at a rate of about 2.0-3.5 mg/kg/min (it falls with prolonged fasting). Obviously if hyperinsulinism is intermittent then hypoglycemia due to overutilization may occur under circumstances where the 24 hour glucose requirement is less than 200 G. In this case the assumption may be incorrectly made that hyperinsulinism is not present.

12. Madison, L. L. and R. H. Unger. The physiologic significance of the secretion of endogenous insulin into the portal circulation. I. Comparison of the effects of glucagon-free insulin administered via the portal vein and via a peripheral vein on the magnitude of hypoglycemia and peripheral glucose utilization. J. Clin. Invest. 37:631-639, 1958.
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15. Garber, A. J., P. H. Menzel, G. Boden and O. E. Owen. Hepatic ketogenesis and gluconeogenesis in humans. J. Clin. Invest. 54:981-989, 1974.

The diagnosis of hyperinsulinism (the fasting insulin:glucose ratio)

he diagnosis of insulinoma requires the demonstration of a plasma insulin concentration which is inappropriately high for the situation in which it is drawn. Traditionally two types of measurements are made: during fasting or after provocative tests. The former would appear to be by far the most reliable. The important point to remember is that in determining plasma insulin values during fasting it is not the absolute concentration of hormone which is important but the insulin concentration relative to the plasma glucose concentration, a point which was first emphasized by Seltzer and co-workers (16). As is well known, insulin secretion is controlled by a complicated feedback system, the most important component of which is the glucose concentration in the interstitial fluid perfusing the pancreatic islets (17). When glucose concentrations rise, insulin release is stimulated; when glucose concentrations fall, insulin release is inhibited. Thus a "normal" plasma fasting insulin value (5-15 μU/ml) may be abnormal in the face of hypoglycemia. The invariant rule in working up hypoglycemia, therefore, is determination of the insulin and glucose concentrations in the same plasma sample taken at the time of hypoglycemia. If the patient does not have hypoglycemia when seen by the physician, then a fast is started in the hospital with hormone and glucose values measured intermittently (every 4-6 hours) for 72 hours or until hypoglycemic symptoms occur, whichever comes first. A typical pattern in insulinoma is shown in Fig 1. If hypoglycemia does not occur by 72 hours it is

Figure 1

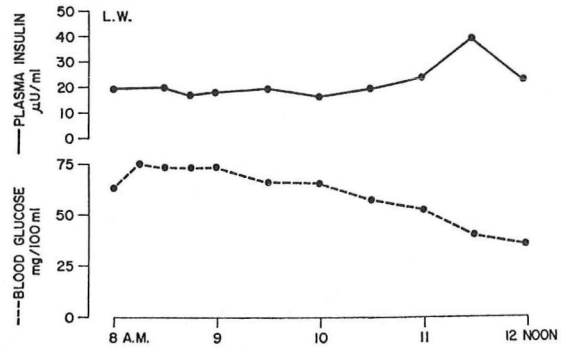


Fig. 1. Levels of plasma insulin and blood glucose during the last four hours of a 12-hour fast in a patient with islet cell tumor.

statistically highly unlikely that an insulinoma is present. Typical insulin:glucose ratios $\left(\frac{\text{plasma insulin, } \mu U/ml}{\text{plasma glucose, mg/100 ml}}\right)$ are shown in Table IV.

Table IV

Fasting insulin:glucose ratios in normal man and in patients with insulinomas*

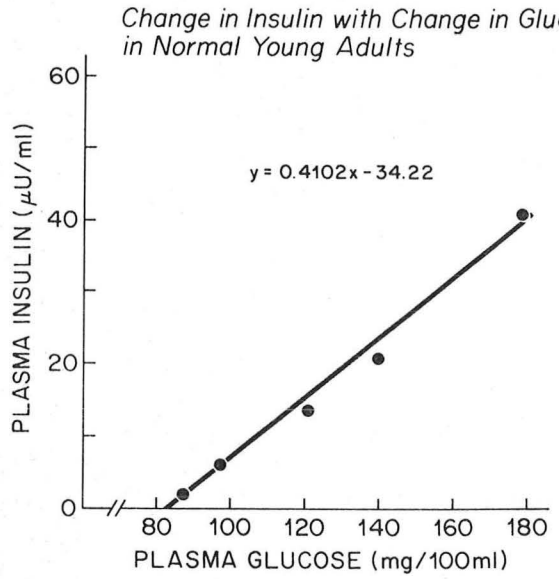
Condition	Type of patient	Insulin:glucose ratio		Ref
		Mean	Range	
Normal	Non-obese (n=11)	0.23 (AM)	--	18
		0.15 (PM)	--	
	Non-obese (n=50)	0.06		19
	Obese (n=12)	0.17		
	Non-obese (n=21)	0.14		16
	Obese (n=11)	0.30,0.43	--	
	Non-obese (n=6)	0.08	--	20
	Non-obese (n=6)	0.20 ± .10	0.07-0.31	21
	Obese women (n=5)	0.28	--	22
	Non-obese (n=10)	0.14 ± .05	0.05-0.23	23
	Infants (n=4)	.03	0-0.08	24
	Non-obese adults(n=7)	.04	0-0.10	
	Non-obese (n=30)	<0.40	--	25
Insulinomas	Children under 12(n=13)	6.5 ± 16.94	0.42-74	26
	Adults (n=19)	0.75 ± 0.72	0.21-3.07	23
	Adults(n=3,34 determinations)	>0.40	--	25
	Adults (n=9)	2.37 ± 1.47	1-4.82	5
	Adults (n=27)	0.68 ± 0.47	.04-1.47	22
	Adults (n=10)	3.52 ± 2.28	0.7 -9.92	27
	Adults (n=10)	1.38 ± 1.65	07 -4.3	23

* Where available results are given as means ± 1 SD for the indicated number.

While it is obvious that some insulinomas have fasting insulin:glucose ratios in the normal range, a ratio greater than 0.40 is highly suggestive of hyperinsulinism, particularly if the absolute glucose concentration is in the hypoglycemic range. Since a great deal of experimental work indicates that the glucose threshold for insulin release is between 50 and 100 mg/100 ml and that insulin secretion falls off rapidly below 90 mg%, plasma insulin should be essentially non-detectable when plasma glucose is below 50 mg/100 ml (28). This point is emphasized by the work of Adams, King, and Schwartz (24) who studied these relationships in normal young men by infusing glucose intravenously at varying rates such that study state glucose concentrations increased

in step wise fashion from 87.8 to 179.6 mg/100 ml. They then measured insulin and glucose concentrations with the results which are shown in Fig 2.

Figure 2



(derived from Adams, King and Schwartz, Pediatrics 41:91-105, 1968)

The regression equation for this line is y=0.4102 X - 34.22. (The standard deviation for the slope and intercept are .0315 and 4.7 respectively.) If y (the insulin concentration) is set at zero, the glucose concentration at the intercept on the X axis turns out to be 83.4 mg/100 ml; put in other words plasma insulin should be undetectable at plasma sugars below this level. When similar calculations were made under non-steady state conditions (IV glucose tolerance test) by the Berson group (20) the equation was

$$y = 0.7371\ X - 70.6$$

indicating that the glucose value at which insulin concentration would be zero should be 95.8 mg/100 ml after insulin secretion had been suddenly stimulated to high levels with subsequent rapid drop off. While not all studies show an 80-100 mg/100 ml cut off point for insulin secretion in man (16), it is safe to say that insulin values should be very low below this level. To reiterate, if the plasma glucose is below 50 mg%, any significant concentration of insulin (>5 μU/ml) is likely abnormal. Calculations of insulin response to oral glucose are extremely complicated because of intestinal stimulatory factors (16,21) and should not be used to calculate insulin:glucose ratios. A comment about obesity is indicated here. While obesity causes insulin resistance (16,17,19,29),it is interesting that fasting insulin:glucose

ratios do not appear to be markedly elevated in the obese state (see above). In contrast, obesity will result in marked elevations of the ratios after glucose or tolbutamide stimulation (Fig 2) into the range found with insulinomas. Interestingly, and contrary to conventional wisdom, obesity occurs in less than half of patients with insulinomas (2)

Figure 3 (ref 19)

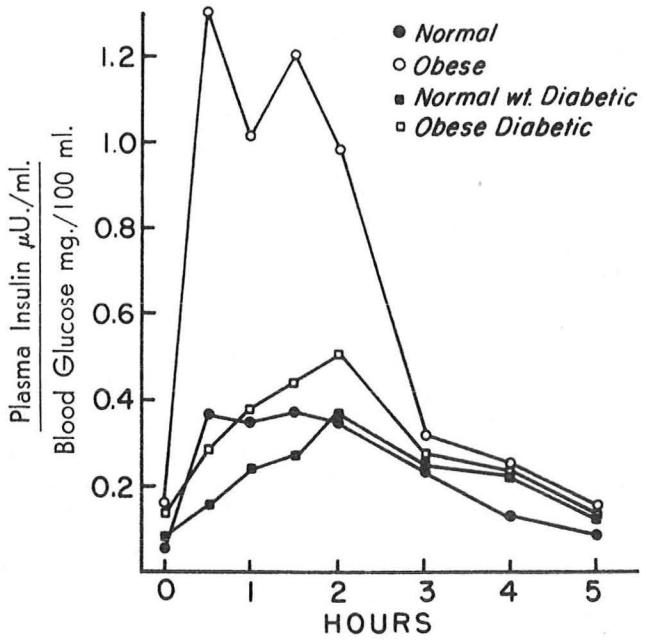


FIG. 7. Plasma insulin response expressed as the index—plasma insulin/blood sugar to oral glucose (100 gm.) of fifty normal, twelve obese, nineteen normal-weight diabetics and sixteen obese diabetic subjects.

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21. McIntyre, N., C. D. Holdsworth and D. S. Turner. Intestinal factors in the control of insulin secretion. J. Clin. Endocrin. Metab. 25: 1317-1324, 1965.
22. Marks, V. and E. Samols. Glucagon test for insulinoma: a clinical study in 25 cases. J. Clin. Path. 21:346-352, 1968.
23. Sherman, B. M., S. Pek, S. S. Fajans, J. C. Floyd, Jr. and J. W. Conn. Plasma proinsulin in patients with functioning pancreatic islet cell tumors. J. Clin. Endocrin. Metab. 35:271-280, 1972.
24. Adams, P. A. J., K. King, and R. Schwartz. Model for the investigation of intractable hypoglycemia:insulin-glucose interrelationships during steady state infusions. Pediatrics 41:91-105, 1968.
25. Grunt, J. A., J. H. Pallota and J. S. Soeldner. Blood sugar, serum insulin, and free fatty acid interrelationships during intravenous tolbutamide testing in normal young adults and in patients with insulinoma. Diabetes 19:122-126, 1970.
26. Castro, A. and N. R. M. Buist. The insulin/glucose ratio in children with islet cell tumors of the pancreas. Clin. Biochem. 7:81-87, 1974.
27. Samols, E. and V. Marks. Insulin assay in insulinomas. Brit. M. J. 1:507-510, 1963.
28. Grodsky, G. M. A threshold distribution hypothesis for pocket storage of insulin and its mathematical modeling. J. Clin. Invest. 51: 2047-2059, 1972.
29. Karam, J. H., G. M. Grodsky and P. H. Forsham. Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. Diabetes 12:197-204, 1963.

It should be emphasized that a normal insulin:glucose ratio on a single occasion does not preclude the diagnosis of insulinoma. While some patients, such as the protocol case, appear to have a semi-fixed level of circulating hormone, in others repeated testing indicates considerable variation. (Table V)

As part of the diagnostic workup proinsulin levels should also be obtained. Proinsulin, the single chain precursor of insulin (Fig 4) is usually present in the plasma to an extent of 20% or less. Under ordinary circumstances proinsulin is split into the C peptide (connecting chain) and insulin prior to storage in the beta cell granules (30) with only a small percentage being secreted into the portal circulation (Fig 5). In patients with islet cell adenomas the percentage of total circulating immunoreactive insulin which is proinsulin may approach high values (23,31-33) as was true of the protocol case (88%) (Fig 6). It is of interest that the tumor tissue itself contains high proinsulin concentrations suggesting some rate-limiting step in the conversion to the insulin molecule (Table VI) (34).

Table V

Repetitive fasting insulin:glucose ratios in patients with insulinoma (ref 27)

Patient	Determination	Plasma glucose	Plasma insulin	I:G ratio
		mg/100 ml	μU/ml	
1	1	20	37	1.85
	2	12	45	3.75
	3	20	51	2.55
	4	32	63	1.97
	5	20	71	3.55
	6	12	119	9.92
	7	15	124	8.27
2	1	68	47	.69
	2	26	121	4.65
	3	28	146	5.21

Figure 4 (ref 30)

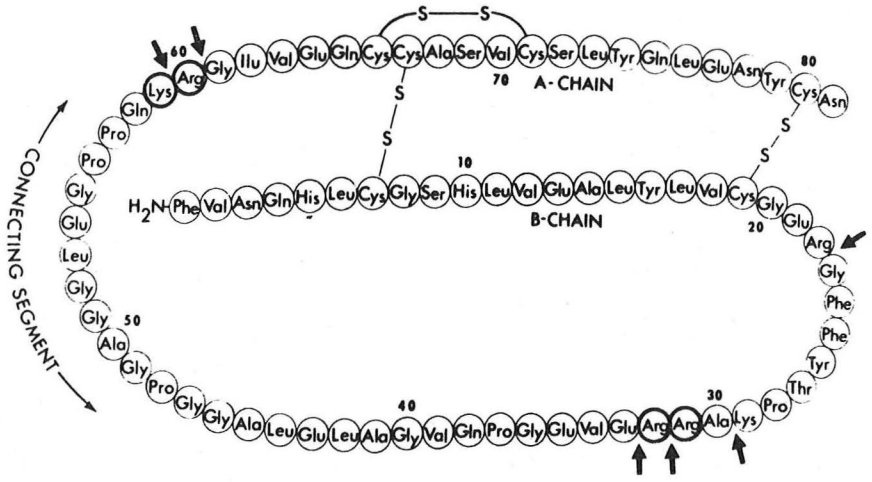
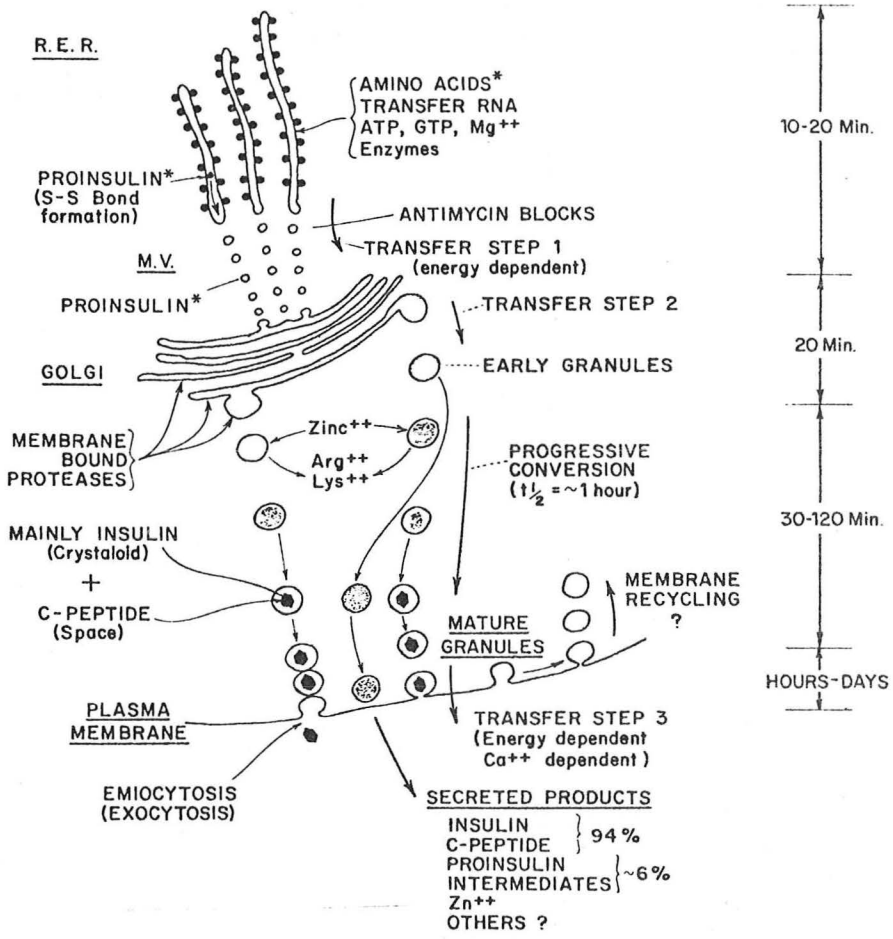


Figure 1. Amino acid sequence of bovine proinsulin. Proinsulin intermediate Form I lacks the Lys-Arg sequence (residues 59 through 60), shown in boldface circles at the C-terminus of the connecting segment. Intermediate Form II lacks the two arginyl residues (positions 31 and 32) at the N-terminus of the connecting segment. Arrows indicate sites of tryptic cleavage. (Reproduced in modified form from (60).)

Figure 4. Schematic summary of the insulin biosynthetic mechanism of the pancreatic beta cells. See the text for a discussion of this process. The time scale on the right side of the figure indicates the time required for each of the major stages in the biosynthetic process. (R.E.R. = rough endoplasmic reticulum; M.V. = micro vesicles.)

Figure 5 (ref 30)



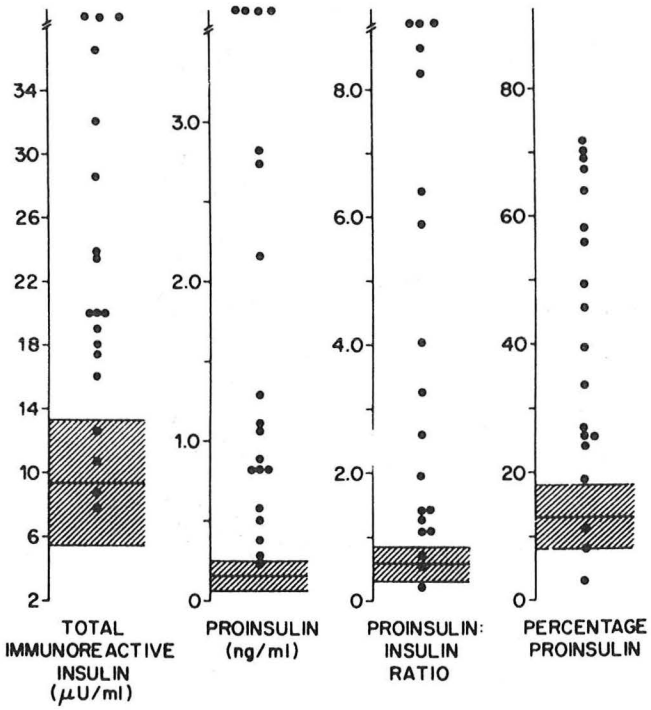


Figure 6 (ref 33)

Table VI

Proinsulin content (%) in adenomas, adjacent normal pancreas and serum (ref 34)

Case	Adenoma	Normal pancreas	Serum
1	12.6	4.8	42
2	18.5	1.9	--
3	19.3	2.4	36
4	22.0	3.2	--
5	5.3	1.7	33
6	15.3	2.8	--
7	7.3	2.3	38
8	14.0	1.8	47
9	9.5	1.8	--
mean ± SEM	13.8 ± 1.89	2.52 ± 0.33	39.2 ± 2.44

30. Steiner, D. F., W. Kemmler, H. S. Tager, and J. D. Peterson. Proteolytic processing in the biosynthesis of insulin and other proteins. Federation Proc. 33:2105-2115, 1974.
31. Gutman, R. A., N. R. Lazarus, J. C. Penhos, S. Fajans and L. Recant. Circulating proinsulin-like material in patients with functioning insulinomas. N. Eng. J. Med. 284:1003-1008, 1971.
32. Gorden, P., B. Sherman and J. Roth. Proinsulin-like component of circulating insulin in the basal state and in patients and hamsters with islet cell tumors. J. Clin. Invest. 50:2113-2122, 1971.
33. Rubenstein, A. H., M. E. Mako, J. I. Starr, D. J. Juhn and D. L. Horwitz. Circulating proinsulin in patients with islet cell tumors. International Congress Series No. 312. Proceedings of the Eighth Congress of the International Diabetes Federation. Excerpta Medica, Amsterdam, 1973. pp 736-750.
34. Creutzfeld, W., R. Arnold, C. Creutzfeld, V. Denticke, H. Frerichs and N. S. Track. Biochemical and morphological investigations of 30 human insulinomas. Correlation between the tumor content of insulin and proinsulin-like components and the histological and ultrastructural appearance. Diabetologia 9:217-231, 1973.

Provocative tests for insulinoma

Should the diagnosis be unclear following the above procedures, provocative tests can be considered. The two most common are the tolbutamide tolerance test and the glucagon test. The leucine infusion test is used much less frequently. The tests are administered as follows.

Tolbutamide tolerance test (35): Dissolve 1 G of sodium tolbutamide in 20 ml distilled water and administer over a 2 minute period. Plasma samples are drawn at 2,5,10,15,20,30,40 and 60 minutes for glucose and insulin determinations. Fifty percent glucose should be available to terminate the test if clinical hypoglycemia supervenes. In the original descriptions of the test a plasma insulin value of 100 μU/ml was considered to be highly suggestive of insulinoma (27) but more recently Fajans has suggested a value of 195 μU/ml (11).

Glucagon test (35): 1 mg of glucagon is given intravenously and plasma glucose and insulin are measured at 0,3,6,10,20,25,30,40,50 and 60 minutes. A value of >160 μU/ml for plasma insulin is considered to be diagnostic though most normals will be below 100 μU/ml (11,35).

Leucine test (35): L-leucine is given orally or intravenously over a 30 minute period at a dose of 0.2 G/kg body wt. Plasma insulin and glucose should be measured at 10 minute intervals for 1 hour. A rise in plasma insulin of 30 μU/ml is considered diagnostic. Illustrative positive examples of these tests are shown in Figs 7-9. (From refs 35 and 36)

Figure 7

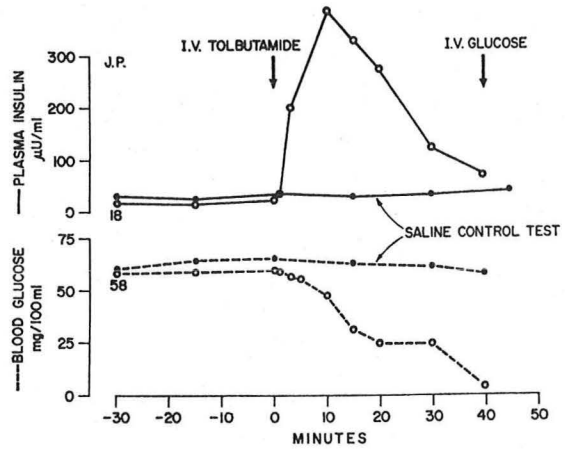


Fig. 3. Effect upon plasma insulin and blood glucose of intravenous administration of tolbutamide to a patient with islet cell tumor.

Figure 8

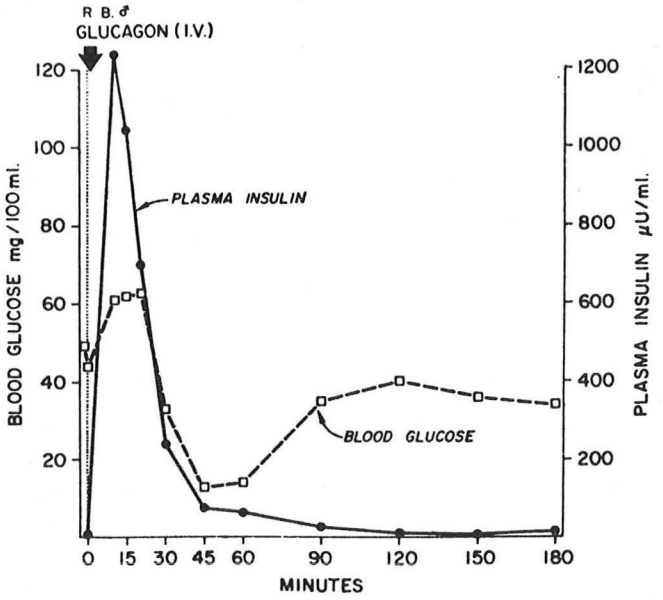
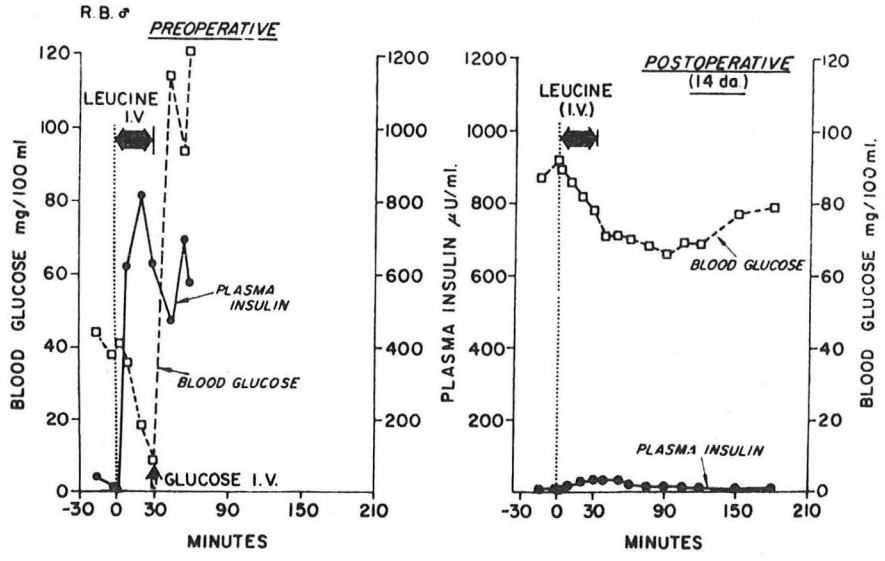


FIG. 3. Effect upon plasma insulin and blood glucose of intravenously administered glucagon before removal of an insulinoma.

Figure 9



Cumulative results from many series reveals tests for insulinoma to be positive in proven cases of functioning islet cell tumors according to the following percentages (Table VII):

Table VII

Positive tests in the diagnosis of insulinoma

(149 authors)

Test	% Positive
Prolonged fasting	95
Tolbutamide tolerance	80
Glucagon test	72
Glucose tolerance test	60
L-leucine test	50

Individual authors report higher percentages of negative results and occasionally false positive tests are seen as indicated by the results of the tolbutamide test in 9 normal patients and 8 islet cell tumors (Table VIII) reported by Gutman, et al (31). Only two of the eight had values greater than 195 μU/ml, the diagnostic value cited by Fajans. The problem of false negative determinations in the tolbutamide test has been emphasized by Khurana, et al (37).

Table VIII

Tolbutamide test in insulinoma (ref 31)

Maximal insulin response (μU/ml)			
Normals		Islet cell tumor	
1	190	1	36
2	103	2	285
3	68	3	323
4	50	4	58
5	100	5	120*
6	76	6	48
7	63	7	123
8	102	8	168*
9	367*	9	--
Mean±SEM	124 ± 33		145 ± 38

* Obese patients

Similar problems exist with the glucagon test. In the paper by Marks and Samols (22), the following results were obtained in 32 patients (Table IX).

Table IX

Glucagon test for insulinoma in 32 patients (ref 22)

Maximum insulin response (μU/ml)	No.
< 100	9
100-130	2
131-160	3
> 160	18

To summarize, the glucagon and tolbutamide tests should be done only if hyperinsulinism cannot be demonstrated under fasting conditions (up to 72 hours). A positive result is helpful if the patient is not obese, but a negative result does not rule out a functioning islet cell tumor. The leucine test and glucose tolerance test should be discarded as diagnostic procedures for insulinoma. (A rare exception for glucose testing would be a patient similar to the one described in ref 9).

35. Fajans, S. S., J. C. Floyd, Jr., R. F. Knopf and J. W. Conn. A comparison of leucine - and acetoacetate - induced hypoglycemia in man. J. Clin. Invest. 43:2003-2008, 1964.
36. Fajans, S. S. Diagnostic tests for functioning pancreatic islet cell tumors. International Congress Series No. 172. Proceedings of the Sixth Congress of the International Diabetes Federation. Excerpta Medica, Amsterdam, 1963. pp 894-897.
37. Khurana, R. C., V. P. S. Dhawer, R. Klayton, D. G. Corredor, Y. Jung, J. C. Sieracki, A. R. Gonzalez and T. S. Danowski. Insulin and glucose patterns in control subjects and in proved insulinoma. Amer. J. Med. Sci. 262:115-128, 1971.

Causes of hyperinsulinism

Once the diagnosis of hyperinsulinism is made, consideration has to be given to the cause, the critical issue being whether the excess insulin has appeared spontaneously or whether it is induced. Factitious hyperinsulinism is not rare and should be especially considered when hypoglycemia occurs in medical personnel such as physicians, nurses and laboratory technicians. The most common method used is surreptitious insulin injection, but patients have also been known to induce hypoglycemia by sulfonylurea ingestion. The former can be detected in one of two ways. First, the plasma may be tested for insulin antibodies (38,39). Since insulin invariably induces antibodies in man after several weeks of injection, their presence in a patient denying use of the hormone is highly suggestive of factitious disease (but see below). A better and more definitive test would be determination of the C-peptide content of plasma since this would tell whether circulating immunoreactive insulin was of exogenous or endogenous origin; i.e., a high plasma insulin with a low C-peptide would mean exogenous administration. Sulfonylureas would cause

C-peptide elevation and would have no antibodies. Definitive proof would require direct measurement of sulfonyurea in the plasma. It is of interest that extrapancreatic tumors causing hypoglycemia are associated with high levels of plasma non-suppressible insulin-like activity (NSILA) (40). Fortunately this material does not cross react in the insulin radioimmunoassay.

38. Berkowitz, S., J. E. Parrish and J. B. Field. Factitious hypoglycemia: why not diagnose before laporatory? Amer. J. Med. 51:669-674, 1971.
39. Service, F. J. and P. J. Palumbo. Factitial hypoglycemia. Three cases diagnosed on the basis of insulin antibodies. Arch. Int. Med. 134:336-340, 1974.
40. Megyesi, K., C. R. Kahn, J. Roth and P. Gorden. Hypoglycemia in association with extrapancreatic tumors: demonstration of elevated plasma NSILA-S by a new radioreceptor assay. J. Clin. Endocrin. Metab. 38: 931-934, 1974.

Characteristics of islet cell tumors

In recent years the concept has developed that islet cell adenomas are derived from primitive neural crest cells which can give rise to a variety of tumors which secrete polypeptide hormones. Since all of these cells have the ability to take up biogenic amines and decarboxylate them, the appelation APUD (amine precursor uptake and decarboxylation) has been applied to them (1). The interrelationship between neural crest cells and these tumors is shown in Fig 10.

Figure 10

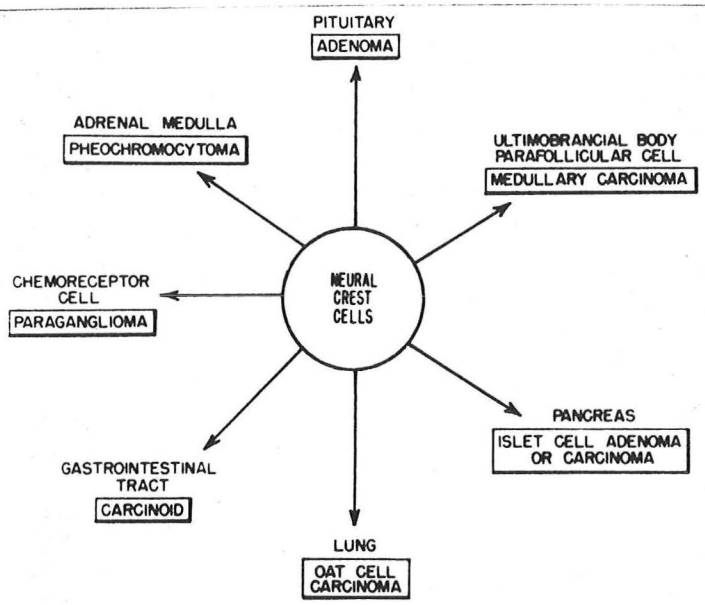


Figure 3. Distribution of polypeptide-hormone-producing cells arising from the neural crest, with associated neoplasms.

It has been appreciated for years that these tumors can coexist in the multiple endocrine adenoma syndromes as illustrated in Fig 4 (Fig 11).

Figure 11

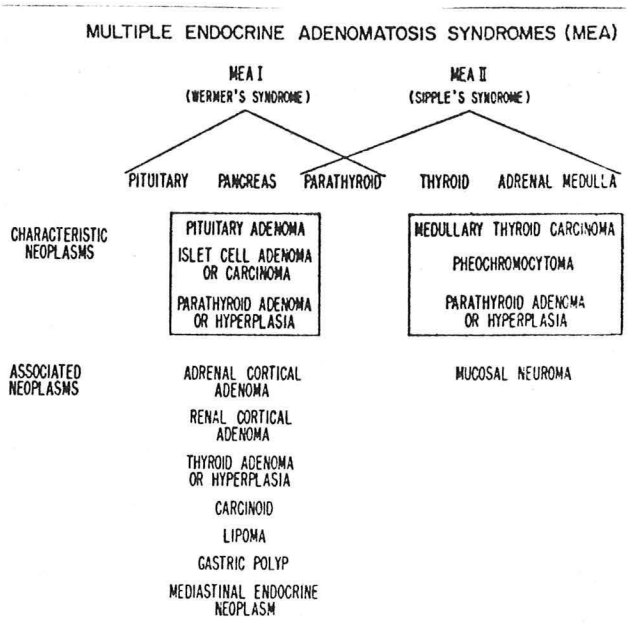


Figure 5. Pathological features of multiple endocrine adenomatosis syndromes.

What may be less well appreciated is the fact that islet cell tumors themselves may secrete more than one hormone (Fig 12). Thus an islet cell adenoma may present as the multiple endocrine adenoma syndrome even though no other adenomas are present.

Figure 12

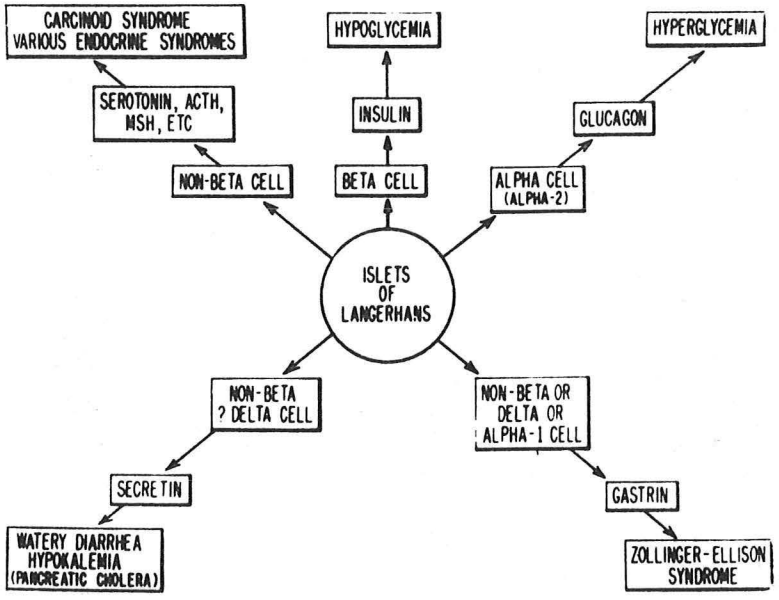


Figure 1. Spectrum of islet cell neoplasms.

The exact incidence of dual (or triple) hormone secretion from the same tumor is not known. Broder and Carter (41), in a study of 52 patients with metastatic islet cell carcinoma, found seven patients with this phenomenon. The most easily identified would appear to be ACTH since these subjects tend to develop skin pigmentation (42). It is of interest that islet cell tumors can cause hypercalcemia (43).

41. Broder, L. E. and S. K. Carter. Pancreatic islet cell carcinoma. I. Clinical features of 52 patients. Ann. Int. Med. 79:101-107, 1973.
42. Walter, R. M., J. W. Ensinck, H. Ricketts, J. W. Kendall and R. H. Williams. Insulin and ACTH production by a streptozotocin responsive islet cell carcinoma. Amer. J. Med. 55:667-670, 1973.
43. DeWys, W. D., R. Stoll, W. Y. Au, M. M. Solisnjak. Effects of streptozotocin on an islet cell carcinoma with hypercalcemia. Amer. J. Med. 55:671-676, 1973.

Insulinomas can appear at any age. There are over 30 cases documented below the age of two (2) and the tumor may be present congenitally (44). About 70% occur between the years of 30 and 60 and the mean age of presentation is 45. The incidence of malignancy is around 20-25%. In most series males and females are about equally affected but in the largest review (2) 40.3% of 1067 patients were male and 59.7% female. Racial breakdowns are hard to come by, but it is of interest that only 1 of 52 patients with islet cell carcinoma was black (41).

44. Rawlinson, D. G. and R. O. Christiansen. Light and electron microscopic observations in a congenital insulinoma. Cancer 32:1470-1476, 1973.

Treatment

The preferred treatment for insulinoma is surgery and the operation of choice is enucleation. However, this is not always easy because many insulinomas are occult and difficult to find at the time of exploration. It now seems clear that arteriography (celiac or superior mesenteric) should be carried out once the diagnosis of hyperinsulinism is made (5,45). The purpose is not diagnosis, since both false positive and false negative tests occur, but localization of the tumor. Pancreatic scanning is of no value. As shown in Table X, approximately two-thirds of proven insulinomas can be identified with angiography.

Table X

Arteriography and pancreatic scans in insulinomas (ref 2)

	Arteriography	Scan
Number of tests	170	81
Number positive	112	15
% Positive	66	19

45. Deutsch, V., R. Adar, E. T. Jacob, H. Bank and M. Mazes. Angiographic diagnosis and differential diagnosis of islet cell tumors. Amer. J. Roent. Rad. Ther. Nucl. Med. 119:121-132, 1973.

Because of the fact that insulinomas may not be found at surgery, even by thorough palpation of the pancreas, the practice of carrying out a 70% distal pancreatectomy has become more or less standard procedure in many centers when the tumor is not found at operation. This recommendation was based on the assumption that most islet cell tumors were located in the tail of the pancreas, an assumption which has proved erroneous. In actuality the distribution is about equal between head, body and tail (Fig 13).

Figure 13

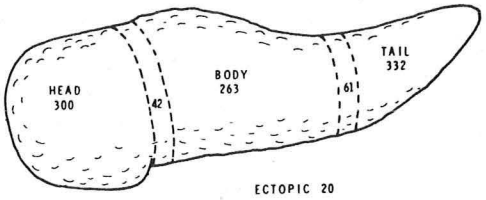


Figure 1. Location of all 1,018 functioning benign and suspiciously malignant insulinomas reported in the English literature.

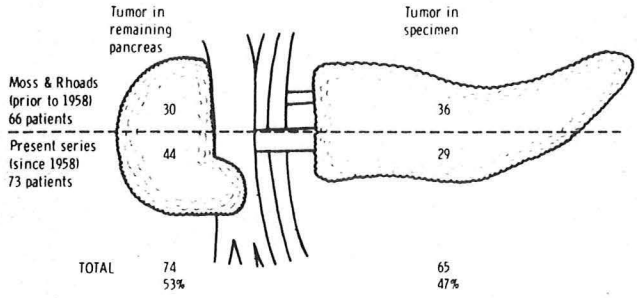


Figure 2. The proved location of all occult insulinomas reported in the English literature. The cases below the dotted line are those reported between 1958 and June 1971.

The problem of the occult insulinoma has been carefully discussed by Mengoli and LeQuesne (47). In 50 cases where distal pancreatectomy was carried out tumor was present in the resected specimen in 11 (22%). Tumor was subsequently found in the non-resected pancreas at a later operation in 24 (48%). In 15 (30%) it was never found, though in 3 cases the diagnosis was thought to be in error. The authors suggest that no further surgery be done if the tumor is not found initially and that a subsequent operation be carried out if

symptoms continue, arguing that continued growth of the tumor may make it easier to find on repeat surgery several months later. This approach seems to be particularly reasonable since about three-fourths of all adenomas are found at first operation (Fig 14) and since there are now at least partially successful means to treat the symptoms medically (see below).

Figure 14

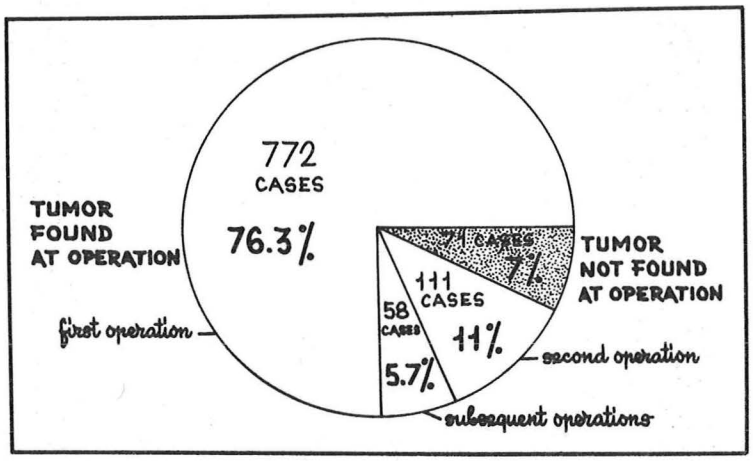


Fig. 2. Possibility of removing beta-islet cell tumors of the pancreas at operation.

It is important to remember that while most islet cell adenomas appear to be single, multiple tumors are not rare. For this reason it is very important to have a glucose analyzer in the operating room. If removal of the tumor does not cause a rise in plasma glucose, a second adenoma should be suspected. About 4% of insulinomas are associated with multiple endocrine adenoma syndromes. Other pathologic characteristics are shown in Table XI.

Table XI

Pathologic findings in 951 cases of islet cell adenoma (ref 2)

Characteristic	Number	Percent
Single	789	83
Multiple	123	13
MEA	39	4
Parathyroid	16	1.5
Pituitary	10	1
Adrenal	10	1
Thyroid	3	0.5
Benign	798	84
Malignant	153	16
Metastases	47	5

The tumors are usually small. Five percent are less than 0.5 cm in diameter, 34% are 0.5-1.0 cm, 53% are 1-5 cm, and 8% are greater than 5 cm. Ectopic locations do occur. (Table XII)

Table XII (ref 46)

TABLE II Location of Ectopic Insulinomas in the English Literature

Location	Number of Cases
Wall of duodenum	5
Near tail of pancreas	3
Gastrosplenic omentum	2
Posterior to tail of pancreas	1
Between head of pancreas and liver	1
Posterior to head of pancreas	1
Paraduodenal	2
Adherent to stomach	1
Spleen	1
Not specified	3

The results of surgery are shown in Fig 15. About two-thirds of cases obtain relief of symptoms with an additional 10% going on to diabetes. The latter represent cases in which the bulk of the pancreas is removed. Sixteen percent have persistent hypoglycemia and 11% die. The cause of death is shown in Fig 16. Postoperative pancreatitis is the most common mode of exodus.

Figure 15 (ref 2)

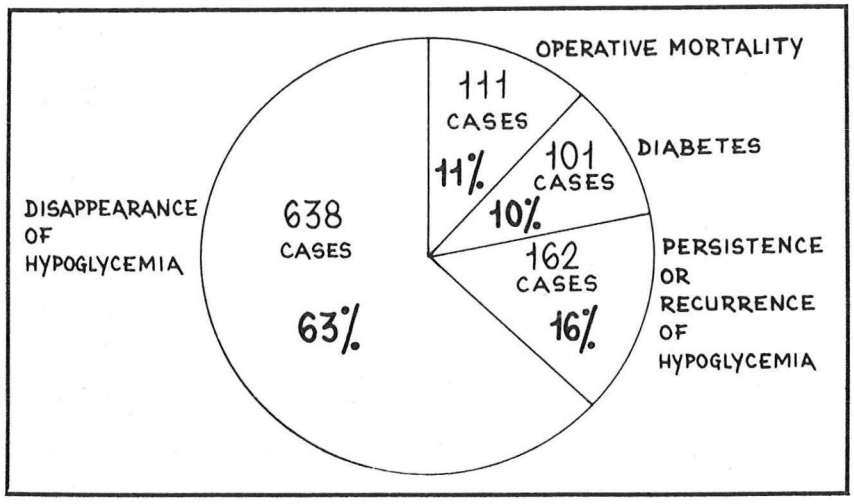


Fig. 4. Long-term results in 1,012 completely documented cases.

Figure 16 (ref 2)

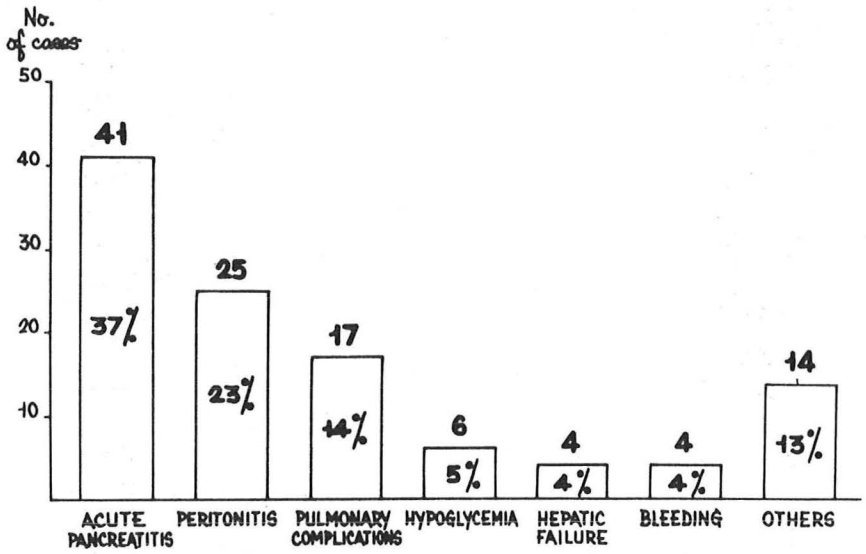


Fig. 3. Operative deaths (111 cases).

Mortality rate as a function of operative procedure is shown in Table XIII; it goes up with the more extensive procedures as expected. The major complications in surviving patients are fistula formation, pseudocysts and pancreatitis. Comparison of the incidence of acute pancreatitis in patients dying and living indicates the grave prognosis associated with the post-operative form of this disease.

Table XIII (ref 46)

TABLE III Postoperative Mortality for All Resective Procedures for Insulinoma Since 1958

Procedure	Number	Deaths	Mortality (%)
Extirpation	297	14	4.7
Distal pancreatectomy	211	10	4.7
Whipple procedure	11	1	9.9
Subtotal pancreatectomy	13	2	15.3
Total pancreatectomy	17	2	11.7

Table XIV (ref 2)

Table IX. *Incidence of postoperative complications in 882 completely documented cases in relation to different interventions*

		Fistulas		*Pseudocysts*		*Acute pancreatitis*		*Other complications*	
	No.	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Enucleation	428	51	12	28	6.5	5	1.2	34	8
Distal resection	335	16	4.5	1	—	11	3.4	20	6
Pancreaticoduodenectomy	61	—	—	—	—	7	12	5	8
Other types of operation	58	—	—	—	—	—	—	9	15

46. Filipi, C. J. and G. A. Higgins. Diagnosis and management of insulinoma. Amer. J. Surg. 125:231-239. 1973.
47. Mengoli, L. and L. P. LeQuesne. Blind pancreatic resection for suspected insulinoma: a review of the problem. Brit. J. Surg. 54:749-756, 1967.

Medical treatment

Medical treatment for insulinoma is indicated only in preparation for surgery or after failure to find the tumor at operation. In order to control symptoms glucose should be given in whatever amounts are necessary to prevent hypoglycemia (preferably to the point of glycosuria). In addition attempts should be made to block insulin release from the tumor. The most effective drug for this purpose is diazoxide (1,48-50). The drug can be given intravenously or orally in a dosage of 300 to 1200 mg per day. While it was ineffective in the protocol case, a high percentage of adenomas do respond and long term treatment is possible.

Figure 17 (ref 49)

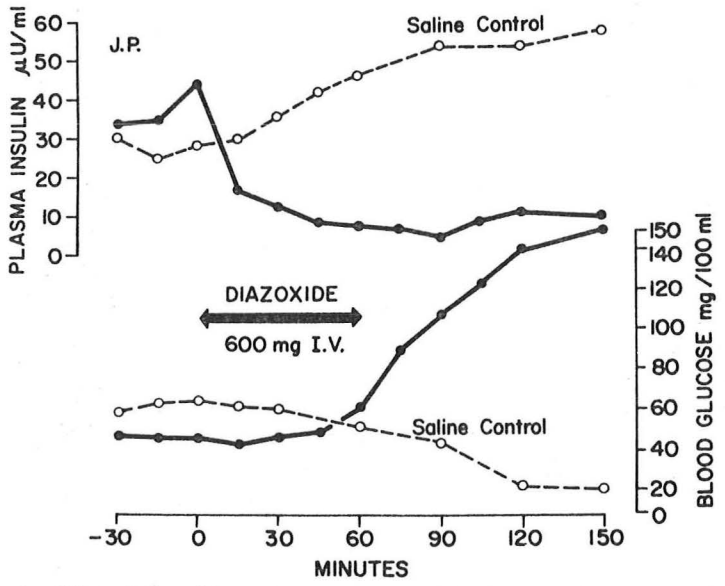


FIGURE 1. Effect of diazoxide on plasma insulin and blood glucose levels in a patient with a functioning pancreatic islet cell tumor.

Diazoxide has powerful sodium retaining effects and must always be given in combination with a diuretic. Its major side effects are shown in Table XV.

Table XV

Side effects of diazoxide in 103 cases (ref 48)

Side effect	Number
Hirsutism	25
GI disturbances	16
Edema	17
Hyperuricemia	11
Tachycardia	9
Hematologic	8
Dermatologic	4
Immunoglobulin ↓	4
Postural hypotension	2
Lymphadenitis	1
Gingival hyperplasia	1
Muscle wasting	1

48. Black, J. Diazoxide and the treatment of hypoglycemia: an historical review. Ann. N. Y. Acad. Sci. 150:194-203, 1968.
49. Fajans, S. S., J. C. Floyd, Jr., C. A. Thiffoult, R. F. Knopf, T. S. Harrison and J. W. Conn. Furthur studies on diazoxide suppression of insulin release from abnormal and normal islet tissue in man. Ann. N. Y. Acad. Sci. 150:261-280, 1968.
50. Seltzer, H. S. and J. R. Crout. Insulin secretory blockade by benzothiodiazines and catecholamines: reversal by sulfonylureas. Ann. N. Y. Acad. Sci. 150:309-321, 1968.
51. Diazoxide: a review of its pharmacologic properties and therapeutic use in hypertensive crises. Drugs 2:78-137, 1971.

Long term glucagon therapy has been used, but the results are not impressive (52,53). More recently diphenylhydantoin has been reported to be effective in some cases (54,55). Incidentally,the administration of Dilantin may interfere with diagnostic studies for insulinoma as pointed out by Knopp, Sheinin and Freinkel (54). This is not a purely hypothetical problem since, as noted earlier, many patients with hypoglycemia and convulsions are misdiagnosed as having epilepsy.

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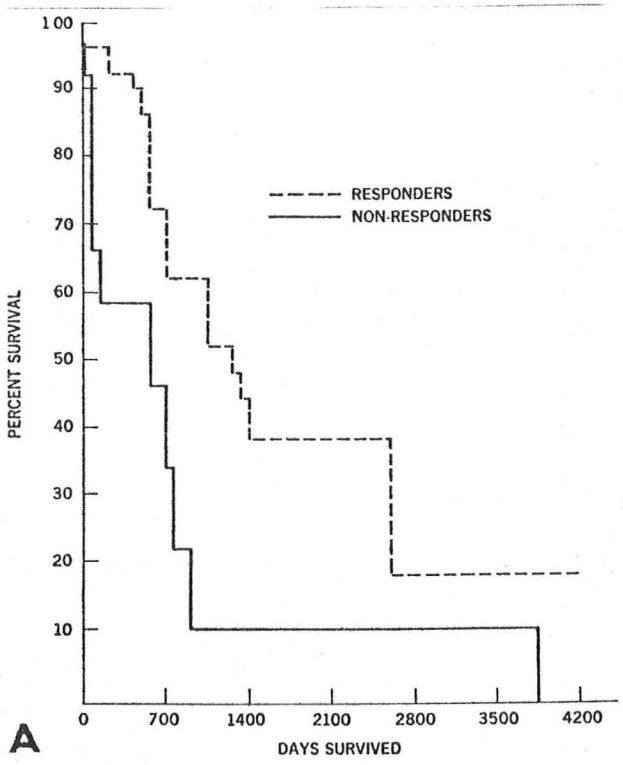
Chemotherapy in islet cell carcinomas

This subject will not be covered in detail. The basic therapeutic agent is streptozotocin, a diabetogenic drug (56,57). It is usually administered at a dose of 0.6 to 1.0 G per m^2 body surface area weekly for a total dose of 2-4 G per m^2. It is toxic and nausea and vomiting occur in 98% of the patients. Renal and hepatic toxicity are observed in about 65% of cases; while usually reversible, 5 of 52 patients died in renal failure (56). In the same series median survival was said to be doubled by streptozotocin in responding patients. About two-thirds of patients are said to show symptomatic or objective improvement.

Figure 18 (ref 56)



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A preliminary report has appeared indicating a modest response to l-asparaginase, but treatment time was only two months and it is not likely to be of significant benefit.

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Hypoglycemia and insulin autoimmunity

In regard to the second case of the protocol, attention is called to a syndrome of apparent autoimmunity to endogenous insulin in which hypoglycemia is a major feature (59,60). While it could not be absolutely ruled out from these reports that the patients had not taken exogenous insulin to induce the antibodies, the evidence was against it. In these cases, when insulin immunoassays were attempted because of hypoglycemia, binding of radioactive insulin was found in the serum prior to the addition of anti-insulin serum for the assay. Huge total amounts of insulin were noted - up to 35,280 μU/ml.

The protocol case was unusual in several ways. First, by capillary muscle biopsy he was a genetic diabetic. Secondly, his early course was characterized by insulin resistance and severe hyperglycemia. Thirdly, he was demonstrated by C-peptide assay to have a pancreas which was capable of vigorously secreting insulin. It was our impression that he was a diabetic who had developed an insulinoma. However, spontaneous reversal of the syndrome makes this unlikely. The best interpretation of his illness would seem to be as follows. He is a genetic diabetic, but does not have insulin deficiency. In the course of a myeloma-like illness he developed autoantibodies to insulin which had the capacity to bind and block biologic activity resulting in apparent development of symptomatic diabetes mellitus. Under the influence of exogenous insulin, antibody production was markedly stimulated and insulin resistance supervened. His own B-cells responded to the insulin resistant state with maximal insulin output. Hypoglycemia then developed either as a result of complete saturation of antibodies or, more likely, as a consequence of spontaneously diminished antibody formation such that large amounts of insulin were released inappropriately.

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