MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

March 25, 1965

PARA-ENDOCRINE SYNDROMES OF NEOPLASIA

The term "para-endocrine" syndrome is often used to designate certain complications which arise in the course of non-endocrine neoplasia and which simulate effects induced by excess of certain hormones. A list of 10 such syndromes and the hormones mimicked, all of them polypeptides, is given in Table I.

It is often inferred that these syndromes result from ectopic hormone synthesis by tumor cells. Theoretically this is possible since all cells are descendants of the same ancestor cell and are endowed with the same DNA containing the same information necessary to synthesize any protein produced by any other cell. In the course of cellular differentiation, repression of the extraneous synthetic functions takes place, but in the biosynthetic chaos of neoplasia a "de-differentiation" occurs and long-repressed synthetic processes may re-emerge.

Proof of ectopic hormone synthesis requires biologic, immunochemical, and physicochemical evidence of increased hormone in tumor and plasma, and, where possible, evidence of target organ effect. Table I reveals that in only one "para-endocrine syndrome", Cushing's syndrome, have these criteria for ectopic hormone synthesis been satisfied. In all other syndromes specific evidence of hormone synthesis by tumor is lacking.

One of the common and perhaps most baffling of the syndromes is severe and often fatal hypoglycemia which complicates certain neoplastic diseases. The following review will delineate the syndrome and attempt to resolve the mystery of the mechanism of tumor hypoglycemia.

CASE #1: [redacted]

A 50 year old [redacted] male developed an anaplastic (oat-cell) bronchogenic carcinoma that produced an ACTH-like substance. The zona fasciculata of the adrenal glands became hyperplastic and hyperfunctional, producing Cushing's syndrome from excessive steroid production. During the course of hospitalization, he developed a gastric ulcer that perforated on two occasions, in spite of adequate initial surgical repair. He later developed severe bilateral bronchopneumonia and acute peritonitis, and then expired.

This was the first [redacted] admission ([redacted]-63) for this 50 year old colored male who developed severe cough, weight loss, weakness and anorexia three to four months PTA. About six weeks PTA he developed ravenous appetite and thirst; drinking as much as "four gallons of water daily", voiding six to eight quarts of urine daily. The weakness and 20 pound weight loss were progressive and he complained of severe dull, low back pain. The pertinent physical findings were signs of recent weight loss and generalized muscular weakness, and egophony in the right upper lung field. A chest film revealed a mass in the right upper lobe with atelectasis and hilar lymphadenopathy. The clinical impression on admission was oat cell bronchogenic carcinoma with Cushing's syndrome.

Hospital Course: Bronchoscopy revealed a granular mass obstructing the right upper lobe main bronchus. The patient continued to put out massive quantities of urine of low specific gravity, averaging 1.004; there was persistent hypernatremia and sodium levels averaging 150 mEq/l. There was persistent hypokalemia with potassium levels averaging 2.5 to 3.0 mEq/l, and CO_2 of 30 mEq/ml. A Fishberg test revealed concentrating ability to 1.012 and the PSP test and BUN were normal. The glucose tolerance test was abnormal but not diagnostic of diabetes mellitus. The PBI was 2.7 ug.%. 17-keto-steroids were 32 and 33 and 17-hydroxycorticoids were 54.7 and 43.4 mg per 24 hours. The diabetes insipidus was resistant to vasopressin. FBS rose gradually to 180 mg% and a diagnosis of mild diabetes mellitus was made. Two weeks before his death the patient developed signs and symptoms of a perforated gastric ulcer. At laparotomy a lesion was found in the lesser curvature of the stomach which had perforated into the lesser peritoneal sac. A feeding jejunostomy was performed and the post-operative course was complicated by bilateral bronchopneumonia. Terminally, the patient developed a metabolic alkalosis, vomiting frequently. He then became hypotensive, comatose, and expired on [redacted]-63 on the 49th day of his hospital course. The clinical impression was an ACTH-producing bronchogenic carcinoma with nephrogenic diabetes insipidus secondary to hypokalemia nephropathy complicated by perforated gastric ulcer and bronchopneumonia.

Autopsy Findings: The necropsy confirmed the clinical and the biopsy diagnosis of oat cell carcinoma of the lung. The pertinent areas of metastases include the hypophysis (including the adeno' and neurohypophysis) and the right and left adrenal glands. The pars distalis and tuberalis and the median eminence were partially destroyed and the infundibular stalk and process were completely destroyed by the metastasis. The cells of the pars distalis contained an occasional hyaline body identical to those described by Crooke resulting from steroid therapy. The cortex of both adrenal glands revealed hyperplasia of the zona fasciculata. The hyperplasia of the fasciculata and atrophy of the zona glomerulosa was indistinguishable from the changes described in Cushing's disease. The renal changes included cloudy swelling and fatty degeneration of the tubules. The findings are essentially identical to those described in other cases (selected references mentioned below) of anaplastic oat cell carcinoma of the lung producing an ACTH-like substance, complicated by diabetes insipidus due to destruction of neurohypophysis.

Additional pertinent findings included a persistent perforated gastric ulcer, a subdiaphragmatic abscess and severe peritonitis involving the lesser peritoneal sac.

Cause of death: Anaplastic (oat-cell) bronchogenic carcinoma.

CASE #2: [redacted]

An elderly colored female with severe hypoglycemia associated with starvation and a massive leiomyosarcoma of the mesocolon with complete replacement of the left lobe of the liver by tumor metastases.

This was the second [redacted] admission for this 82 year old [redacted] female who was admitted on [redacted]-63 in a semicomatose state, in great pain and unable to swallow. She was first seen in 1961 when she came to the EOR complaining of nausea and vomiting, severe abdominal pain, and a mass which had been present in her abdomen for several years. She was found to have a large firm mass which extended from the suprapubic area to just below the umbilicus and was thought to have an infarcted leiomyoma. An exploratory laparotomy revealed a large tumor mass, thought to be retroperitoneal, for which she received 3500 roentgens without response. The patient did well, symptomatically, however, until one year ago when she came into the [redacted] complaining of severe left shoulder pain, and an x-ray of this area revealed an osteolytic lesion of the left humeral head. She progressively deteriorated over the past six months, and 10 days prior to admission had a convulsion. She had been semicomatose since that time.

Physical examination revealed a cachectic, obtunded elderly female with a BP of 170/90, pulse of 84, and respirations of 20, temperature 95.4° rectally. She was semicomatose with marked pitting edema of the lower extremities extending up to the sternum and forehead. The left border of cardiac dullness was within normal limits. The heart sounds were distant. Breath sounds were diminished bilaterally and there was bilateral basilar rales. A large abdominal mass extending from the suprapubic area to the umbilicus was palpated despite marked ascites. The left shoulder was tender. The clinical impression was intermittent hypoglycemia and retroperitoneal neoplasm.

Laboratory Studies: Hgb 9.1, Hct 30, WBC 7,000 with 89 polymorphonuclear leukocytes, 10 lymphocytes and 1 eosinophil. Urine: pH 6, negative for albumin and sugar. The VDRL was negative and the BUN was 23. Determinations of the blood glucose which were performed every four to six hours were 30, 35, 100, 29, 100, 254, 114, and 150 mg%. The chest plate revealed an osteolytic lesion in the left humeral head and neck, and evidence of bilateral pleural effusion.

Hospital Course: Glucose in water was administered at the rate of 17 grams per hour (408 g/d) for the remainder of the patient's hospital stay. The patient continued to deteriorate, and died on [redacted]-63.

Autopsy Findings: A large pinkish white tumor mass measuring approximately 25x15x10 cm was found to be arising from the mesocolon. Microscopically it appeared very cellular tumor with coarse granular nuclei, marked pleomorphism, and multiple mitotic figures, as well as occasional tumor giant cells. The cytoplasm between the nuclei was very pale and slightly fibrillar. There were only occasional areas of collagen fibers in what was considered to be a leiomyomasarcoma.

An incidental finding was a grade II adenocarcinoma of sigmoid colon which had grown into the attached sarcoma. However, there was no evidence of lymph node or liver involvement by the adenocarcinoma. The entire left lobe of the liver, which weighed 2950 g, was occupied.

CASE #3: [redacted]

The patient was an elderly male admitted because of hypoglycemic coma and hemiparesis relieved by glucose. Removal of a large retroperitoneal fibrosarcoma was followed by relief of hypoglycemia, with post-operative "diabetes" lasting one week. Four years later hypoglycemia reappeared in association with metastases which were removed, and again transient "diabetes" appeared and hypoglycemia was diminished.

Studies during the post-operative remission of the hypoglycemia revealed a decreased rate of glucose utilization after IV glucose and a diabetic response to tolbutamide. Tumor contained 800 U of ILA (fat pad) which could not have been due to insulin since by radioimmunoassay only negligible quantities were measurable.

This 78-year old man was admitted to the hospital in [redacted] 1958, because of a right-sided hemiparesis and coma that suddenly developed 12 hours after his last meal. All signs and symptoms cleared, however, after a glucose infusion was begun. Ten days later he had a similar episode. The blood sugar on this occasion was found to be 18 mg per 100 ml. He again responded rapidly to an infusion of glucose. Hypoglycemic attacks subsequently became very frequent, and almost constant intravenous therapy with glucose was required.

An abdominal mass was noted, and at operation a 2700-gm. retroperitoneal fibrosarcoma was found and removed (Fig. 1). Transient hyperglycemia and glycosuria were present for one week after operation.

Subsequently, the patient was asymptomatic from the standpoint of hypoglycemia until 1962 when hypoglycemic attacks, characterized by confusion, weakness, aphasia and agitation began. These were triggered by even mild exercise after a fast of 4 or 5 hours. Multiple high-protein feedings had little, if any, effect on the symptoms. He was, therefore, readmitted to the hospital in [redacted] 1962, and again underwent surgical exploration.

Three large fibrosarcomatous masses, 2 in the pelvis and 1 near the pancreas, but not contiguous with it, were found. Tumor nodules were also noted on the mesentery and liver. A total of 802 gm. of tumor was removed. Again, the patient demonstrated transient hyperglycemia after operation.

Convalescence was complicated by homologous-serum hepatitis but no return of the hypoglycemia.

The patient was next admitted to the Clinical Research Center at the University Hospital in Birmingham, on [redacted] 1963, for investigational purposes. Incomplete small-bowel obstruction developed 12 hours after admission. An exploratory laparotomy was performed, and the obstruction relieved by lysis of adhesions in the region of the distal jejunum and proximal ileum. A mesenteric tumor implant was removed and noted by the pathologist to possess the same morphologic characteristics as the tumor previously removed. Convalescence was uncomplicated, and 2 weeks later

an intravenous glucose tolerance test, utilizing 25 gm of glucose and rapid administration was performed. The disappearance rate was 2.3 per cent per minute (normal, greater than 3 per cent per minute), but serum insulin, as determined by the immunoassay of Yalow and Berson, rose only slightly (from 0 to 15 uU/ml). An oral leucine tolerance test utilizing 150 mg. of D-L leucine per kilogram of body weight was performed. Blood glucose did not fall below the pre-test value of 50 mg% and serum insulin did not rise above 5uU/ml. An intravenous tolbutamide tolerance test is distinctly abnormal in that it is diabetic in type during the first 30 minutes by the criteria of Unger and Madison; FBS was 75 mg% and the 20-minute value was 62 mg%. But a rather brisk insulin response was noted (25 to 75 uU/ml). Tumor homogenate was assayed for insulin-like activity (ILA) by the bioassay of Martin and Renold. The tumor was found to contain approximately 1 U of ILA/g of tissue, both by glucose conversion to CO_2 and by the allegedly more specific glucose-to-glycogen conversion. Thus, the entire tumor of 802 gm. contained 800 units of insulin-like activity. Was this insulin-like activity due to insulin or to non-insulin substances in the tumor tissue? The comparison of insulin-like activity in the fibrosarcoma with that of a functioning pancreatic insulinoma, 2 milliunits of beef insulin and 2 milliunits of human insulin reveal the sarcoma to have 1/2,000 the per weight ILA of the insulinoma. However, antibeef insulin antibody inhibited stimulation of carbon dioxide production from C-labeled glucose by both insulinoma and sarcoma.

Radioimmunoassay of tumor extract revealed of insulin. Since "insulin" which is neutralizeable by antiserum should react in an immunoassay, the ILA neutralized could not have been insulin. It must have been either an insulin potentiator or an insulinoid substance which could not operate when insulin is totally neutralized by antibody.

CASE #4: [redacted]

Undifferentiated anaplastic bronchogenic carcinoma without known para-endocrine manifestations. Yet his hepatic metastases contained 300 U of positively identified insulin, and 0.5 mg of glucagon, the only tumor ever reported to contain immunoassayable hormone.

This was the first DVAH admission of this 50 year old [redacted] male who was transferred from an osteopathic hospital because of intermittent back pain of 12 months duration. His history includes easy fatigability and decreased appetite for approximately four months PTA. During this time, however, he had not been acutely ill and had continued to work. According to his wife he was breathing very rapidly on admission to the osteopathic hospital approximately two weeks prior to his transfer to the [redacted]. Just as he was to undergo spinal fusion, having been told that he probably had a ruptured disc, a routine chest film revealed extensive nodularity throughout the lung fields, and he was transferred to the [redacted] as a consequence.

Physical examination revealed a middle-aged, slightly obese, [redacted] male breathing at a rate of 50 per minute. He was faintly cyanotic and was very pale. He was unable to walk and was incontinent of urine. His blood pressure was 188/100, pulse 120. Pertinent physical findings included a slight increase in the AP diameter of the chest without abnormalities in percusion. There were diffusely scattered dry rales and coarse rhonchi throughout the chest. The liver was palpable 3 fingerbreaths below the right coastal margin across the entire abdomen. The remainder of the examination was non-contributory.

Hospital Course: Patient remained extremely dyspneic and confused and was found dead on the second day of his admission. The admission lab results were as follows: Hgb 9.2, Hct 30, WBC 16,000, BUN 28, SGOT 170, SGPT 65. There were two blood sugars recorded - 115 and 165 mg %; however, it is not known whether the patient was truly fasting at these times. The significant findings include lungs with multiple tumor nodules, the largest one found in the right apex and measuring 9 cm in diameter. This appears to be the primary lesion. Numerous secondary nodules are scattered throughout both lungs. On section - the tumor masses appear to be well circumscribed partly neprotic and are reddish brown yellow with hemaragic areas noted. The liver weighed 3290 grams and several metastases measuring up to 6 cm in diameter were noted. The right adrenal gland was partially replaced by metastatic tumor. The microscopic examination revealed an undifferentiated pleomorphic carcinoma of the large cell type, the primary lesion being in the right upper lobe bronchus with metastases to both lungs. There were hemorrhagic infarcts within the tumor masses and viable tumor at the peripheral portions of these infarcts. Similar tumor was found both in the hepatic metastasis and in the adrenal metastasis. Neither the pituitary gland nor the islets of Langerhans were unusual in appearance.

TABLE I - Para-Endocrine Syndromes of Neoplasia

Syndrome and Suspected Hormone (M.W.)	Tumor	Evidence of Hormone Excess				
		In Plasma		In Tumor		
		Bioassay	Immunoassay	Bioassay	Immunoassay	Target Organ Effect
Cushing's ACTH (4500)	Bronchogenic and oat cell carcinoma, malignant thymoma, Pancreatic and islet cell carcinoma	↑	↑	↑	(See Jarrett)	+
Gelhorn-Plimpton PTH (10,000)	Carcinoma of liver, kidney, ovary, pancreas, breast, malignant lymphoma	?	-	-	?	+?
Hyperthyroidism TSH (30,000)	Carcinomas of bronchus, G.I. tract, prostate, choriocarcinoma, lymphoma, leukemia		-		-	±
Water Retention ADH (1084)	Anaplastic bronchogenic or oat cell carcinoma	(Urine)	-		-	
Hypoglycemia Insulin (6,000)	Fibrosarcoma, adrenocortical, liver and G.I. carcinoma	0	0	0 (?)	0	
Precocious Puberty Gonadotropin (30,000)	Hepatoblastoma	(Urine)	-	-	-	+
Gynecomastia Prolactin (26,000)	Carcinoma of bronchus	-	-	-	-	+
Osteoarthropathy HGH (27,000)	Carcinoma of bronchus	-	-	-	-	+?
Zollinger-Ellison (?) Gastrin (13,430)	Islet cell carcinoma	-	-		-	+?
Erythrocytosis (?) Erythropoietin (30,000)	Hypernephroma, fibromyoma, hepatoma, cerebellar, hemangioblastoma, sarcoma	?	-	?	-	+?

TABLE II - HYPOGLYCEMIC TUMORS

Tumor Type: (Number Reported)	Size	Age & Sex	Weight Loss	Coexisting Disorders
MESODERMAL				
Mesenchymal* (49)	Massive (700-10,000g.); metastases uncommon	Old 70% males	Usually slight except when metastases are present	Neurofibromatosis, acromegaly, splanchnomegaly, idiopathic masculinization.
Adrenocortical carcinoma (13)	Massive; hepatic metastases common	Young	Extensive hepatic metastases are present.	Cushings, virilism, 11-B-hydroxylase deficiency, splanchnomegaly, gynecomastia.
ENDODERMAL				
Hepatoma (28)	Massive (3100-5200g. livers); 50-80% of liver replaced	Middle-aged male, Negro	Emaciated	Polycythemia
Cholangiocarcinoma (5)	Massive liver involvement	Middle-aged	Emaciated	-
Gastric Ca (2)	Massive; few liver metastases	Middle-aged	Emaciated	-
Ca of cecum (1)	Massive	Elderly	Emaciated	Testicular feminization.

*Mesenchymal - 80% malignant

Types:
a. Spindle cell fibrosarcoma and, less commonly, benign fibroma --most common.
b. Leiomyosarcoma, rhabdomyosarcoma are rarer.
c. Mesothelioma, pseudomyxoma peritonei (not malignant).
d. Liposarcoma and neurofibroma.
e. Reticulum cell sarcoma, leukemia, rare.

Growth: Metastases occur but not commonly; slow growth is characteristic.

Location: Anatomically related to mesothelial surface (72% to peritoneum, 28% to pleura). Of 29 cases, 10 were retroperitoneal, 4 originated from kidney, 4 from liver, 4 from thorax, 2 from ovary or uterus, and the rest from assorted viscera.

Histology: Striking similarity of all "mesenchymal" tumors despite varying diagnoses: (1) Spindle cells of apparent low-grade malignancy; (2) Scattered hyaline collagen-like masses.

CLINICAL FEATURES COMMON TO ALL

1. Hypoglycemia, usually very severe (9-40%), fulfills Whipple's criteria, occurs late (10 months or less before surgery or death) in the course of a massive (600-10,000 g.) tumor or an obviously advanced malignancy.

2. Presenting symptoms are due either to the hypoglycemia or to the malignancy. (Eg., hunger accompanying advanced malignancy suggests either this diagnosis, islet cell carcinoma, or insulinoma and coexisting extra-insular malignancy). Bizarre CNS symptoms of hypoglycemia are often wrongly attributed to cerebral metastases.

3. Differential diagnosis: Cancer with starvation; islet cell carcinoma. Insulin radioimmunoassay permits differentiation from beta-cell tumors.

TABLE III

	Normals	Extra-pancreatic neoplasms	Beta-cell neoplasms
Mean Fasting insulin level	19±7.5 uU/ml (2-63)	Normal or low (only reported exception: Oleesky's patient with 860 uU/ml)	Usually rises
Hourly insulin level	Rises only after meals	Remains in fasting range, even after glucose!	Wide spontaneous fluctuations
Mean insulin 20 min after IV Tolbutamide	40 uU/ml (27-89)	Little or no change (<40)	160-300 uU/ml
Insulin response to leucine	Little or no change	Little or no change	Usually rises

4. Treatment: Glucose, steroids, glucagon; removal of tumor and, at times, radiation or chemotherapy, may cause remission. Subtotal pancreatectomy doesn't help. DDD may be tried in adrenocortical carcinoma.

MECHANISM(S) OF HYPOGLYCEMIA: THEORIES (Figure 1)

THEORY (1): BETACYTOTROPIN RELEASE FROM TUMOR

(NOTE: Known betacytotropins include glucose, ribose, certain keto-acids and amino acids (leucine, isovaleric acid), sulfonylureas).

THE DATA: Although a keto-acid, p-OH-phenyllactic acid, was found in high concentration in the urine of Sellman's mesothelioma patient and the leucine content of the same patient's tumor was extremely high, plasma ILA was normal. Except for Oleesky's case, plasma insulin has always been normal or low by radioimmunoassay, and injection of tumor extract into rabbits causes no hypoglycemia (Sellman, Nevius).

CONCLUSION: No evidence of a betacytotropic effect.

THEORY (2): INSULIN RELEASE FROM TUMOR

a. Tumor is actually a beta-cell tumor in disguise: Although Skillern was impressed by the "glandular" arrangement of cells in a fibrosarcoma with hypoglycemia, and Karsh reported that an islet cell carcinoma had "metastasized" as a spindle cell tumor, there is no evidence to favor this theory.

b. Tumor is the site of ectopic insulin synthesis: Insulin has never been identified immunochemically in the tumor of a hypoglycemic patient.

(NOTE: Insulin in enormous quantities has been specifically identified in a tumor, a bronchogenic carcinoma, only once (Unger), but this patient (Case #4 in the protocol) was not known to have hypoglycemia. Increased plasma insulin has been found only once (Oleesky) in a hypoglycemic fibrosarcoma patient, but this result is now questioned. Boshell has found 800 U of insulin-like activity, neutralizable with insulin-antibody, in the fibrosarcoma of Case #3; however, we have assayed this same tumor by immunoassay and it contains negligible amounts of insulin; therefore, it is probable that Boshell's activity was either a potent potentiator of insulin or an insulinoid which was inactive in the total absence of insulin).

c. Tumor acts as a "hormone sponge": Because glucagon, as well as insulin, was present in the hepatic metastases of Case #4, it was suggested that this tumor might be deficient in hormone degrading enzymes and might have been "taking up" these hormones at a rate which exceeded its capacity to destroy them, acquiring in time enormous quantities (Unger). If so, tissue breakdown might cause their release. Since Case #4 was not known to be hypoglycemic, the relationship of this case to hypoglycemic tumors, none of which have contained extractable insulin, is questionable.

THE DATA: No hypoglycemic tumor has ever been found to contain immunoassayable insulin (Table IV).

CONCLUSION: Hypoglycemia associated with tumors is not caused by release of insulin from the tumor.

THEORY (3): INSULINOID RELEASE FROM TUMOR (Insulinoid is any material which mimics, at least in part, the action of insulin in lowering blood glucose concentration (eg. Hypoglycin, THAM):

1. "Silverstein Factor" - An acetone-extractable fraction from fresh Walker carcinomas, BW 5147, or OG-2 tumors of mice caused hypoglycemia when injected into normal and diabetic mice. Similar fraction from normal tissues had no such activity.

TABLE IV MEASUREMENTS OF INSULIN AND INSULIN-LIKE ACTIVITY (ILA) IN HYPOGLYCEMIA ASSOCIATED WITH TUMORS

Tumor Type		Radioimmunoassay		Bioassay			
		Plasma Insulin	Tumor Insulin	Plasma ILA		Tumor ILA	
				Fat Pad	Diaphragm	Fat Pad	Diaphragm
MESODERMAL							
Fibrosarcoma	NOT INCREASED	9	7	* 6	2	9**	8
	INCREASED	1	-	1	3	6	3
Adrenocortical Carcinomas	NOT INCREASED	-	-	* 1	0	1	-
	INCREASED	-	-	-	1	-	-
ENDODERMAL							
Hepatoma	NOT INCREASED	-	-	* 1	1	1	-
	INCREASED	-	-	-	-	1	-
Gastric Carcinoma	NOT INCREASED	-	-	* -	1	-	1
	INCREASED	-	-	-	-	-	-
Cecal Carcinoma	NOT INCREASED	-	1	* 1	-	1***	1***
	INCREASED	-	-	-	-	-	-

* Less than 10 U ILA per tumor.
** Although one tumor contained 16 U of ILA, the author (Steinke) states that this is normal for tissue extracts.
*** Although the author (Tranquada) stated that ILA was increased, total tumor ILA was only 5.64 U.

its characteristics: (1) Water soluble (2) Non-dialyzable (3) Doesn't withstand freezing (4) Acetone extractable (5) Histochemical tests indicate that DNA is an important constituent of this fraction.

2. Roffo-Corea factor - Extracts of spindle cell sarcoma of rabbits cause hypoglycemia when injected IV in rabbits, 8-12 U/500 g. (adequate data not given, however).

3. In vitro ILA - Whitney, Miller, August, Boshell, Tranquada, Perkoff have recovered ILA, which is not insulin by immunoassay, from 9 of 26 hypoglycemic tumors, both by rat epididymal fat pad and by rat hemidiaphragm technics (Table IV)(See Appendix). The variation may have been explained by Whitney (confirmed by Perkoff) who found a dialyzable inhibitor of ILA. The unmasked ILA is (1) Water soluble (2) Non-dialyzable (3) Extractable in acid-alcohol or buffer (4) Heat stable.

4. ILA was present in serum of a patient with hypoglycemic fibrosarcoma until removal of the tumor (Whitney).

CONCLUSION: Strong evidence for an "insulinoid" in tumors, often masked by an inhibitor. (NOTE: However, "insulinoid" and an insulin potentiator would be indistinguishable in the foregoing studies).

THEORY (4): INSULIN POTENTIATOR IS RELEASED FROM TUMOR

Substances thought to potentiate insulin by unknown mechanisms include versenate, manganese, biguanides, salicylates, and ortho-cresotinic acid. In addition, insulin potentiation by inhibition of insulin degradation is attributed to insulinase inhibitors such as tryptophane and indole acetic acid.

THE DATA: Although an analysis of tumor tissues for such compounds has not been made, insulinase activity of both tumor and liver of Sellman's patient did not differ from that of rat liver and no inhibition of insulinase activity was noted. However, the previously cited findings of Boshell could be interpreted as insulin potentiation. All data which supports the insulinoid theory can be invoked in support of an insulin potentiator theory.

CONCLUSION: Insulin potentiation is possible; insulinase-inhibition unlikely.

THEORY (5): INCREASED TUMOR GLYCOLYSIS

THE EVIDENCE:

1. Enormous glucose requirements of some patients: This indicates increased glucose utilization somewhere. (See Appendix I).

2. Elevated coefficient (k) of a glucose assimilation (Oleesky). The k is usually low in normoglycemic cancer patients (Marks)

3. Arteriovenous (A-V) glucose difference across a hypoglycemic fibrosarcoma: August:41 mg% (242-201 mg%) - (A glucose infusion was running and the study is open to question). If the tumor blood flow was from [redacted] ml/100g/min, a range considered likely by Eisenberg, then tumor utilized 48-240 g/d. of glucose; but Butterfield found no A-V glucose difference. but no data is given and arterial glucose may have been too low for a measureable difference.

4. In vitro glucose uptake by fibrosarcoma slice (Perkoff): Tumor utilized 0.2 mg/ of glucose/100 mg of tumor/hour, or 48 g/d. Uptake was maximal without insulin!

5. Suppression of glycosuria in diabetic tumor hosts: Walker carcinoma in rats caused rapid amelioration of diabetes (Ingle); hypoglycemia in mice with leukemic tumors which concentrate radioglucose (Silverstein).

6. Increased blood lactate levels in 3 of the 4 cases in which measurements were made (August , Landau , Tranquada , Hayes).

7. Veno-arterial lactate difference across fibrosarcoma (August) was 24.5 mg% (44.8 - 20.3 mg%), or 27-135 g/d of lactate produced by tumor.

NOTE: Neoplastic cells are characterized by abnormally high levels of glycolysis (Warburg), the cause of which may be a deficient Pasteur effect. In normal tissues, lactic acid production is decreased in the presence of O_2; the ATP generated by respiration inhibits phosphofructokinase (PFK), the rate limiting enzyme of glycolysis; respiration, too, comes to a rest. However, in tumor cells and in other rapidly growing tissues, the Pasteur effect is deficient. ATP is depleted by protein synthetic energy requirements, and ADP stimulates PFK. Furthermore, normal cellular membrane barriers to glucose penetration do not exist, and tumor cells are freely permeable to glucose even though insulin is low (either because of an intrinsic cell membrane problem or because of the presence in tumor ECF of insulinoid or insulin potentiator).

CONCLUSION: Data is scattered and faulty. Still it is probably true 1) that neoplasms in general utilize increased quantities of glucose 2) that glucose utilization by tumors is not under the same controls as normal tissues 3) and that in large tumors increased glycolysis could account for hypoglycemia. BUT: why do only rare patients with these unusual and often slowly growing tumors develop hypoglycemia; why doesn't every patient with widespread malignancy become hypoglycemic with fasting? Increased glycolysis, if related to rate of protein synthesis and, therefore, common to all tumors doesn't explain this.

THEORY (6): DECREASED COUNTER-REGULATORY HORMONES

THE DATA: Growth hormone (Yalow) and steroids are normal in tumor hypoglycemia; glucagon hasn't been measured. In adrenocortical carcinoma with adrenogenital or Cushing's syndrome, growth hormone suppression by steroids is possible.

CONCLUSION: Counterregulatory hormone response in most cases of tumor hypoglycemia is probably normal.

THEORY (7) TUMOR INHIBITS HEPATIC GLUCOSE PRODUCTION

a. By replacement of hepatic tissue by tumor: Experimentally at least 80% of liver tissue must be destroyed in order to produce hypoglycemia. Yet, most of the mesenchymal tumors with hypoglycemia had no hepatic involvement, and of the adrenocortical and endodermal tumors in which hepatic metastases were the rule, at least 20% of liver tissue was generally present. Furthermore, in bronchogenic and GI cancers with extensive replacement of liver tissue, hypoglycemia rarely, if ever, occurs (Lowbeer).

But, in hepatomas with hypoglycemia, in which an estimated 40-95% of liver is replaced, a unique combination of circumstances may be posulated: 1) the uninvolved liver is usually cirrhotic or alcoholic, and may be incapable of full compensation 2) since normal liver cells lack a glucose-impermeable cell membrane (Cahill), glucose uptake by malignant liver cells might exceed that of other malignant tissues - but they lack glucose-6-phosphatase (Landau) and fructose-1, 6, disphosphatase, hence have lost the ability to produce glucose.

CONCLUSION: A possibility only in extensive liver involvement, especially in hepatomas.

b. By humoral inhibition hepatic glucose production (HGO): Like insulin, an insulinoid material or a powerful insulin potentiator could inhibit HGO, at any or all points (glucose-6-Pase activity, glycogenolysis, gluconeogenesis).

(NOTE: Hypoglycemia caused by alcohol (Freinkel, Madison), valeramide (Dulin), and perhaps by ethionine (Combes and Schenker) is the result of HGO inhibition alone (alcohol, and perhaps ethionine, decrease gluconeogenesis).

CONCLUSION: A possibility (see section on insulinoid).

c. By non-humoral inhibition of HGO: Diversion of gluconeogenic substrates: Reduced gluconeogenesis could result from diversion of amino-acids from liver to tumor for protein synthesis.

(NOTE: Diversion has been invoked to explain FBS-lowering effect of the anabolic steroid methandrostenolone (Dianobol) in normal subjects and in experimental diabetes (Landon). Growth hormone and/or ACTH suppression by steroid might also explain FBS lowering).

Amino acids in normoglycemic rats with Walker carcinomas are normal except for glutamine which was low in plasma, liver, and muscle.

THE DATA: HGO has been measured only once, in a hepatoma patient. It was less than 30% of normal (See Appendix I).

CONCLUSION: a) An absolute decrease in HGO has been measured in a hypoglycemic hepatoma patient. b) A relative decrease in HGO can be inferred from inability of some patients to compensate for a doubled or tripled rate of glucose utilization (400-600 g/d), a not unreasonable demand for a normally functioning liver. c) High blood lactate implies hepatic dysfunction. Therefore, even if tumor glucose utilization is high, as it may be in all advanced malignancy, compensatory failure of the liver stamps it as an accomplice in the genesis of hypoglycemia, certainly in the hepatoma patients, and possibly in all hypoglycemic cancer patients.

THE RIDDLE OF TUMOR HYPOGLYCEMIA

Because of the crucial role of glucose as the obligatory substrate of the brain, blood glucose homeostasis is tightly regulated. There is but one hormone of glucose abundance concerned with glucose storage within cells as fat and glycogen, insulin, but there are at least 5 hormones of glucose lack designed to extrude or exclude glucose from tissues in which it is not essential; this may reflect the adaptive advantage provided by maximal and multilateral protection of the 115 g. of glucose which the brain demands each day. Glucagon (glycogenolytic and gluconeogenic), cortisol (gluconeogenic), and epinephrine (glycogenolytic) adjust hepatic glucose production to glucose need, while growth hormone, steroids, epinephrine and perhaps other hormones block peripheral glucose uptake while providing alternative substrates (FFA, ketones) for muscle. Enzymatic alterations provide additional protection.

A large tumor with frantic and unrestrainable glucose utilization is like an extra brain or two (Reichard calculated in normoglycemic cancer patients daily glucose production of 242 g., instead of the normal 161 g., a 50% increase). Although the maximal limit of hepatic and renal glucose production is not certain (probably 5x normal, 1000g/d) it seems unlikely from the few available measurements that many tumors would outstrip the compensatory capacity of an intact liver and kidney - and, if they did, then evidence of maximal compensation should be present - but isn't. We doubt that many hypoglycemic tumors use >1000/d, i. e., "eat" their own weight in sugar; why can't liver prevent hypoglycemia?

(The famous patient of Luft with mitachondrial deformity of muscle and uncontrolled cellular respiration (BMR 200) required 5,000 calories daily to maintain weight, yet fasted for 36 hours without becoming hypoglycemic; severe hyperthyroids maintain normoglycemia despite increased CHO metabolism).

Chronic hypoglycemia probably almost always involves a failure of the multilateral counterregulatory system, either 1) due to inadequacy of pituitary, adrenocortical, or alpha cell hormone secretion 2) due to overpowering of counter-regulatory mechanisms by excessive insulin activity, as in insulinoma. Since excess insulin is excluded, only insulinoid or insulin potentiator seem possible. Either of these theories would explain all of the following features of tumor hypoglycemia, all of which occur in insulinoma, including the manifestations of inadequate counterregulatory response:

Inadequate lipolytic response

1. Preservation of body fat. Most fibrosarcoma cases are well-nourished unless extensive hepatic involvement is present.

2. Normal or low plasma FFA levels (Froesch, Hayes, Samols).

Inadequate glycogenolytic response

3. Apparent preservation of hepatic glycogen stores despite hypoglycemia.

Inadequate gluconeogenic response

4. High blood lactate levels. This reflects, at least in part, a failure of the liver to expand Cori cycle activity and convert the increased lactate emerging from the tumor to needed glucose. Insulinoid could block the hypertrophy of gluconeogenic enzymes (Figure 4- 1, 2) necessary to convert the increased lactate load from the tumor to glucose (phosphoenol-pyruvate carboxykinase 1, fructose-1-6-diphosphatase 2).

Increased hepatic glycolysis

It may also reflect increased glycolysis by liver. Insulinoid could raise the normally low rate of hepatic glycolysis (<20% of glucose-6-PO4 pool goes to lactate) by stimulating phosphofructokinase (Figure 4 - 3), the rate-limiting step. Thus decreased lactate metabolism and increased lactate production by liver could explain the hyperlactatemia.

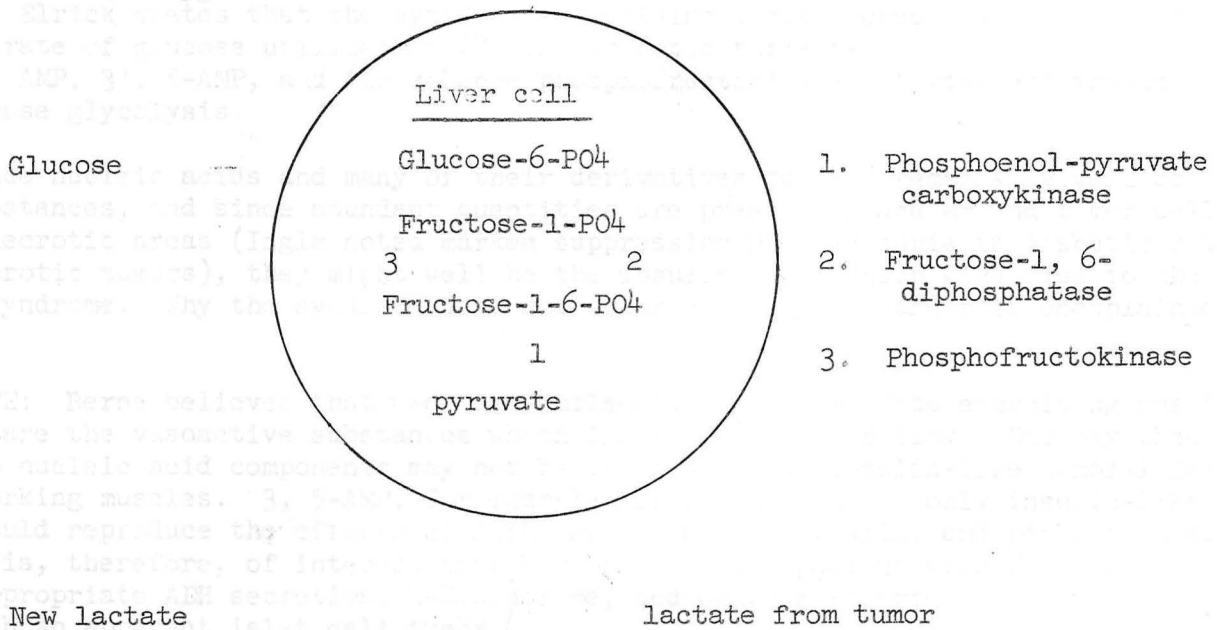

Figure 4 - Hepatic Lactate Metabolism

5. Evidence of increased glucose utilization (high K).

6. Tumors with insulin-like activity but no insulin. Only Theories #3, (insulinoid) or #4 (insulin potentiator), can explain all these findings.

7. Lack of rise in plasma insulin after oral glucose. An excess of insulinoid or potentiator would suppress beta cell secretion.

8. "Diabetic" glucose tolerance for 2-3 hours after oral glucose, with hypoglycemia reappearing after 3 hours (Hayes, Samols). Marked hyperglycemia and glycosuria, can be induced by glucose infusion of from 28-270 g/hr. (Landau, Tranquada). Yet Seltzer found that in normal subjects, glucose infusions of 30 g/hr., failed to elevate blood glucose concentration above 100 mg%.

Therefore, it would seem that the maximal capacity for glucose utilization of some of the tumor patients is below normal, perhaps because of intense counterregulatory hormone response and/or enzymatic changes in normal tissues, as in "starvation diabetes". (Persistance of these futile compensatory adaptations may explain the "transient diabetes" of Case #3 (Boshell) following removal of the tumor). Unlike insulin in starvation, insulinoid release is not increased by glucose abundance or decreased by glucose lack; consequently high levels of counterregulatory hormones may cause "funneling" of glucose to the tumor rather than to muscle and fat, thus lengthening glucose disposal time because of the limitations of tumor blood flow.

CLUES AS TO THE NATURE OF THE INSULINOID

1. Silverstein believed DNA to be an important constituent of his hypoglycemic fraction extracted from mouse tumors.

2. DNA has hypoglycemic activity comparable to the mouse tumor fraction of Silverstein when injected in mice.

3. According to Dole, RNA, adenylic acid and adenosine have the following insulin-like actions on fat in vitro: 1) Suppression of lipolytic effects of epinephrine growth hormone and ACTH 2) Increase in glyceride, fatty acid synthesis and CO_2 production from glucose 3) Increase in lipogenesis from acetate.

4. Elrick states that the cytidine and uridine administered together by vein increased the rate of glucose utilization (K) in cirrhotic patients.

5. AMP, 3', 5-AMP, and ADP enhance phosphofructokinase activity and should, thereby, increase glycolysis.

Since nucleic acids and many of their derivatives qualify remarkably well as insulinoid substances, and since abundant quantities are present in and around tumor cells, leaking from necrotic areas (Ingle noted marked suppression of glycosuria in diabetic rats with small necrotic tumors), they might well be the insulinoid(s) which give rise to the hypoglycemic syndrome. Why the syndrome does not occur commonly in cancer is unexplained, however.

NOTE: Berne believes that there are nucleosides released from exercising muscle and that they are the vasoactive substances which increase its blood flow. One may then wonder if such nucleic acid components may not be the mysterious insulin-like humoral factor produced by working muscles. 3, 5-AMP, for example, could explain not only insulin-like effects but could reproduce the effects of ACTH, glucagon, vasopressin, and perhaps other hormones. It is, therefore, of interest that Kipnis has had a patient with Cushing's diabetes, inappropriate ADH secretion, Z-E syndrome, and Gelhorn-Plimpton syndrome associated with an apparent islet cell tumor.

APPENDIX

I. Glucose Balance: Hepatic glucose output has been estimated only once in a hypoglycemic hepatoma patient (Landau), both by direct measurement of splanchnic glucose balance and by measurement of glucose-C^{14} decay. It was low. Splanchnic balance became negative at an arterial glucose level of 40 mg%, and calculated HGO was 0.5-1 mg/kg/min, (normal HGO 1-3 mg/kg/min). Reduction of HGO alone doesn't explain the enormous glucose requirements reported in both mesodermal and endodermal tumor patients (300-2200 g/d) since a constant glucose infusion of 170 g/d should maintain normoglycemia in a totally hepatectomized person under basal conditions. Reichard et al calculate that 0.78% of the glucose pool is utilized each minute in fasting resting subjects, a rate of 9 g. of glucose per hour. In Landau's patient's HGO was only 1.2 - 3.6 g/hr., a net deficit of 5.4 - 7.2 g. of glucose/hr. assuming normal peripheral glucose utilization. If body weight is 60 kg. and the glucose space 20-50% body weight, the glucose pool would be 12-30 g. Thus 18-60% of the glucose pool might be lost each hour on the basis of this reduction in HGO, peripheral glucose utilization remaining constant, and the blood sugar level could fall below 50 mg% in from 1 to 3 hours or so after a meal. But even if HGO was 0, a constant glucose infusion of 9.0 g. hr. should maintain the glucose concentration.

But in Landau's case an 18 g/hr. infusion of glucose was needed to prevent hypoglycemia. In Sellman's case 12.5 g/hr. were barely able to prevent hypoglycemia. Tranquada's case required 12.5 - 70 g/hr. by constant infusion, "to maintain glycosuria". Glucose utilization must, therefore, be increased. In most cases, however, glucose utilization is probably less than 600 g/d.

However, the livers of these patients are obviously not preventing hypoglycemia when glucose is withheld and one would guess that the normal liver should be capable of at least doubling or tripling its 9 g/hr. (216 g/d) HGO estimated to occur normally in the basal state, i.e., 600 g/d. On the basis of our estimate of tumor glucose utilization, this would have prevented hypoglycemia in most of the reported cases. So impaired compensatory response by the liver is an important factor.

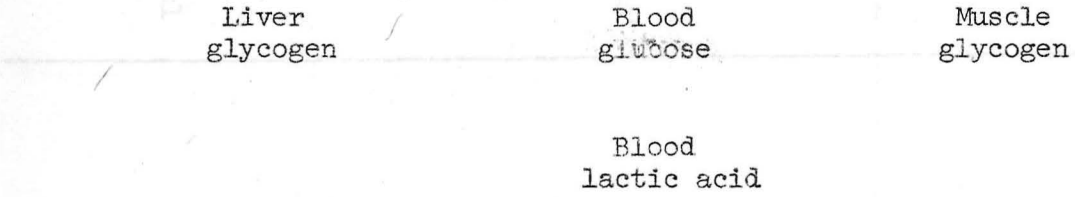

Figure 5. The Cori Cycle

II. Lactate Balance: Normally 12-20% of HGO is derived from lactate (Reichard), i.e., 1 - 1.8 g/hr. or 24-43 g/d. (This percent might rise with diversion of amino from liver to tumor and increased lactate production by tumor). One would expect that the liver would convert the increased lactate to glucose and, through augmented Cori cycle activity, avert hypoglycemia. Yet of 4 hypoglycemic tumor patients in which serum lactate was measured (August, Landau, Tranquada, and Hayes) only one had a normal value. Tranquada's patient had a level of 107 mg%. August's patient's tumor is estimated to have produced 27-135 g of lactate daily or 1 - 5.6 g/hr., almost enough to correct the hypoglycemia. Yet this excess lactate was not utilized by the liver (Figure 3). Why not? 1) Perhaps lactate load exceeded hepatic lactate clearance rate or metabolic capacity 2) More likely, some humoral material from tumor inhibits gluconeogenesis. (NOTE: As suggested in Figure 3 a hyperlactaturia could result if renal function is normal, causing a potentially serious energy leak. Could this be a cause of weight loss in neoplasia, which unless anorexia is present, is not otherwise explained? Metabolic rate is not sufficiently increased in cancer to explain the negative energy balance, and a lactate waste would explain this, "Lactate Diabetes".

TABLE IV
MEASUREMENTS OF INSULIN-LIKE ACTIVITY (ILA) AND INSULIN IN
NEOPLASMS ASSOCIATED WITH HYPOGLYCEMIA

Type of Neoplasm	Laboratory	PLASMA			TUMOR		
		ILA		INSULIN	ILA		INSULIN
		Rat Fad	Rat Diaphragm	Radioimmunoassay	Rat Fad	Rat Diaphragm	Radioimmunoassay
MESODERMAL Fibrosarcoma	Murphy	700 m/U/ml ("normal")	-	-	0.2-3.0 U (total)	-	-
"	Nevius	-	-	-	- 0*	-	-
"	Miller	-	-	-	-	0	-
"	"	-	-	-	10.8U (total)	0.02-2.1 (total)	
"	Stauffer	-	-	-	0	-	32 mU (total)
"	August	-	-	-	600 U (total)	-	-
"	Whitney	"elevated"	"elevated"		"elevated"	"elevated"	-
"	Olecsky	-	-	860 uU/ml	-	-	-
Fibrosarcoma or leiomyoma	Volk	"normal"	"normal"	-	-	20 U (total)	-
Mesothelial Cell Sarcoma	Sellman	"normal"	"normal"	-	0 0*	0	-
Fibrosarcoma	Boshell	"normal"	-	25 uU/ml	800 U	-	1.98 mU/g
Fibrous mesothelioma	Garfield	-	75 uU/ml	-	-	0	-
Fibrosarcoma	Hayes	128 uU/ml	269 uU/ml		-	-	-
Paraganglioma	Field	-	-		-	0.02-0.24 (total)	0

*Extract injected into rabbits

MEASUREMENTS OF INSULIN-LIKE ACTIVITY (ILA) AND INSULIN IN NEOPLASMS ASSOCIATED WITH HYPOGLYCEMIA

Type of Neoplasm	Laboratory	PLASMA			TUMOR		
		ILA		INSULIN	ILA		INSULIN
		Fat Pad	Rat Diaphragm	Radioimmunoassay	Fat Pad	Rat Diaphragm	Radioimmunoassay
MESODERMAL							
Fibrosarcoma 1	Berson	-	-	0			
" 2	"	-	-	11	-	-	-
" 4	"	-	-	0	-	-	0
" 5	"	-	-	0	-	-	0
" 6	"	-	-	-	-	-	64 uU/g
" 7	"	-	-	-	-	-	42 uU/g
Reticulum cell Sa 3	"	-	-	2	-	-	-
Fibrosarcoma	Perkoff	-	-	10 uU/ml	-	present	0
Fibrosarcoma	Froesch	normal	-	-	negligible	-	-
"	Steinke 1,2,3,4,5	-	-	-	-	4.3-162. U (total)	-
Adrenal cortical Ca	Eymontt	180 uU/ml	-	-	.35 uU/g	-	-
"	Williams	-	normal	-	-		
ENDODERMAL							
Hepatoma	Landau	"high normal"	-	-	0	-	-
"	Schonfeld	-	100 uU/ml	-	212 U (total)	-	-
Gastric sarcoma	Gonzales	-	"normal"	-	-	1 U (total)	-
Cecal carcinoma	Tranquada	-	0		" 4+ " (2 mU/g)	" 4+ " (1/10 of pancreas)	0
Fibrosarcoma Bronchogenic carcinoma Colon carcinoma	Floyd	-	-	"low normal"	3-24 mU/g	0.02-2 mU/g	-

REVIEW ARTICLES

I. Para-Endocrine Syndromes in General

Bower, B. F., and Gordon, G. S., Annual Review of Medicine, In Press, 1965. "Humoral Effects of Non-Endocrine Tumors".

deGennes, L., Bricaire, H., et Leprot, J. La Presse Medical, 70:2137, 1962 "Las Syndromes Endocrinieus Paraneoplastique. II. Hypothyroides et Endocrinopathies Diverses"

Gold, G. L. and Shnider, B.I., Ann. Internal Medicine 51:890, 1959,"Some Unusual Syndromes Associated with Neoplastic Disease"

II. Hypoglycemic Tumors

Lowbeer, L., American Journal Clinical Pathology 35:233, 1961. "Hypoglycemia Producing Extrapancreatic Neoplasms"

Silverstein, M. N., Wakim, K. G., Bahn, R. C., American Journal of Medicine 36:415,1964, "Hypoglycemia Associated with Neoplasia"

III. Case Reports of Hypoglycemia Associated with Mesodermal Tumors

A. Mesenchymal Tumors:

Andreew, D., Goranow, I., and Krastinow, G., Endokrinologie, 38:167-174 (1959), "Hypoglycemia in an intrathoracic fibroma"

Arkless, H. A., Med. Bull. Veterans Administration, 19:225-229 (1942),"Coincidence of Rhabdomyofibroma of diaphragm, idiopathic hypoglycemia and retroperitoneal sarcoma"

August, J. T., and Hiatt, H. H., New Eng. J. Med, 258:17-20 (1958), "Severe Hypoglycemia Secondary to a Nonpancreatic Fibrosarcoma with Insulin Activity"

Barjon, P., and Labauge, R., Presse Medicale, 69:2635-2638 (1961), "Les Tumeurs Mesenchymatenses Hypoglycemiantes"

Boshell, B. R., Kirschenfeld, J. J., and Soteres, P. S., New Eng. J. Med., 270:338-341 (1964) "Extrapancreatic Insulin-secreting Tumor"

Bousvaros, G. A., Brit. Med. J., 1:836-838 (1960) "Hypoglycemia in Metastatic Fibrosarcoma of the Liver"

Butterfield, W. J. H., Kinder, C. H., and Mahler, R. F., Lancet 1:703 (1960), "Hypoglycemia Associated with Sarcoma"

DeCoster, A., Payfa, M., Bellens, R., Conrad, V., and Bastenie, P. A., J. Franc. general de med. Chir. Thor. 16:191 (1962) "Intrathoracic Tumor and Hypoglycemia"

Doege, K. W., Ann. Surg., 92:955-960 (1930), " Fibrosarcoma and Mediastinum"

Duncan, G. G., and Schless, G. L., Metabolism 10:200-203 (1961), "Massive Retroperitoneal Fibrosarcoma, Spontaneous Hypoglycemia and Generalized Splanchnomegaly - Report of Case "

Fikenscher, T. F., and Blom, P. S., Nederl. Tijdschr. geneesk 107:1076-1083 (1963) "Hypoglycemia and Fibrosarcoma"

Field, J. B., Keen, H., Johnson, P., and Herring, B., J. Clin. Endocrinology 23:1229-1236 (1963), "Insulin - like Activity of Nonpancreatic Tumors associated with Hypoglycemia"

Floyd, J. C., Power, L., Rull, J., Fajans, S. S., and Conn, J., Clin. Res. (abstract) 11:297 (1963), "Insulin and ILA in Tissue Extracts and Plasma of Patients with Nonpancreatic tumors associated with Hyperglycemia"

Frank, H. A., J. Thoracic Cardiovascular Surg., 44:321-329 (1962). "Intrathoracic Tumors Associated with Hypoglycemia"

Frantz, V. K., Bull. N. Y. Acad. Med., 37:73-74 (1961), " Extrapancreatic Tumors Associated with Hypoglycemia "

Friesen, E. R., and Miller, D. R., Am. J. Surg., 99:420-423 (1960), "Fibrogenic mesodermal tumors an unusual cause of hyperinsulinism"

Froesch, E. R., Burgi, H., Ziegler, W., Bally, P., and Labhart, A., Schweiz. Med Wschr., 92:1250-1255 (1963).

Garfield, C. R., Belcher, H. V., Shuttleworth, J. S., JAMA 181:380, (1962) "Fibrous Mesothelioma with Hypoglycemic Psychosis and Coma"

Hayes, D. M., Spurr, C. L., Felts, J. H., and Miller, E. C., Metabolism 10:183-199 (1961), "Von Recklinghausen's Disease with Massive Intra-Abdominal Tumor and Spontaneous Hypoglycemia: Metabolic Studies before and after Perfusion of Abdominal Cavity with Nitrogene Mustard"

Hines, R. E., Med. Bull. Veterans Administration 20:102-105 (1943), "Hypoglycemia Apparently due to Retroperitoneal Sarcoma"

Holten, C., Acta. Med. Scand., 157:97-102 (1957).

Howard, J. E., Veterans Administration Tech. Bull., 8:1-19 (1955), "Differential Diagnosis and Therapy of Spontaneous Hypoglycemia"

Howard, J. W., and Davis, P.L., Delaware Med. J., 31:29-34 (1959), "Retroperitoneal Hemangiopericytoma Associated with Hypoglycemia and Masculinization"

Kipfer, Helvet. Med. Acta., 24:556-560 (1957).

Kantrowitz, A., Bull. N. Y. Acad. Med., 37:75 (1961), "Extrapancreatic tumors associated with Hypoglycemia - Discussion by Abraham Kantrowitz"

Leger, L., Sors, C., Dubost, C., Magdelaine, M., Lejeune, J., Roseau, E., and Lemaigre, G., Presse Med., 71:219-222 (1963), "The hypoglycemia of extra-pancreatic mesenchymal tumors"

Macnaughton, M. C., and Priest, E. A., Lancet 1:204-205:1297 (1960), "Hypoglycemia Associated with Retroperitoneal Leiomyosarcoma".

Maier, H. C., and Barr, D., J. Thoracic Cardiovascular Surg., 44:321-329 (1962) "Intrathoracic Tumors Associated with Hypoglycemia"

Miller, D. R., Bolinger, R. E., Janigan, D., Crockett, J. E., Friesen, S. R., Ann. Surg., 150:684-696 (1959), "Hypoglycemia due to Nonpancreatic Mesodermal Tumors"

Murphy, R., Med. Clin. N. Amer. 47:391, (1963), "Hypoglycemia with an Extra-pancreatic Neoplasm"

Nesbitt, K. A., Boswell, M. A., Gonzales, deJ., Sarkisian, S. S., Am. J. Clin. Path. 30:148-157 (1958), "Malignant Mesothelioma associated with Hypoglycemia"

Nadler, W. H., and Wolfer, J. A., Arch. Internal Med., 4:700-710 (1929), "Hepatogenic hypoglycemia associated with primary liver cell carcinoma"

Nevius, D. B., and Friedman, N. B., Cancer, 12:1263-1269 (1959) "Mesothelimoas and Extraovarian Thecomas with hypoglycemic and Nephrotic syndromes"

Oleesky, S., Bailey, L., Samols, E., and Bilkus, D., Lancet 2:378-380 (1962), " A Fibrosarcoma with hypoglycemia and a high serum insulin level"

Paulson, G. S., Feehan, J. J., and Westaby, R. S., S. Dakota J. Med. Pharm. 14:5-12 (1961), "Severe Hypoglycemia due to Mesothelioma Arising in Plural Cavity - Case Report "

Pedersen, J., Lund, F., and Ringsted, J., Acta Endocrin, 34:148-156 (1960), Nordisk med., 82:1642-1644 (1959), "Hypoglycemia in the Presence of Massive Fibrosarcoma (Mesenchymoma) "

Perkoff, G. T., and Simons, E. L. Arch. Int. Med. 112:589, (1963) "Hypoglycemia in a Patient with a Fibrous Tumor"

Rosenfeld, E. D., Arch. Path. 48: 255, (1949) "Peritoneal Pseudomyoma"

Porter, M. R., and Frantz, V. K. , Am. J. Med, 21:944 (1956) " Tumors Associated with Hypoglycemia - Pancreatic and Extrapancreatic"

Rossman, E. M., Arch. Internal Med., 104:640-642 (1959) "Mediastinal Neurofibrosarcoma Causing Hypoglycemia"

Scholz, D. A., Woolner, L. B., and Priestly, J. T., Ann. Internal Med. 46:796-807 (1957) "Spontaneous Hypoglycemia Associated with Fibrogenic Tumor: Report of two Cases"

Schmidt, H. W., and Schurholz, K., Deutsch. Med. Wochschr. 86:2231 (1961).

Seckel, H. P. G., J. Clin. Invest. 18:723-731 (1939) "Postmortem Hepatic Glucogenolyas in Hyperinsulinism and Glycogen Diseases "

Sellman, J. C., Perkoff, G. T., Null, F. C., Kimmel, J. R., and Tyler, F. H., New Eng. J. Med. 260:847-852 (1959) "Hypoglycemia Associated with Massive Intro-abdominal Mesothelial-cell sarcoma"

Silvis, R. S., and Simon, D. S., New Eng. J. Med. 254:14-17 (1956) "Marked Hypoglycemia associated with Non-pancreatic Tumors"

Skillern, P. G., McCormack, L. J., Hewlett, J. S., and Crile, G., Diabetes 3:133-140 (1954) "Hyperinsulinism due to Cell Tumors Simulating Sarcoma"

Staffierri, J. J., Cames, O., and Cid, J. M., J. Clin. Endoc. 9:255-267 (1949). "Corticoadrenal Tumor with Hypoglycemic Syndrome, Goitre, Synecomastia and Hepatosplenomegaly"

Stauffer, J. M., Granville, G. E., and Law, S. W., New Eng. J. Med. 265:979-982 (1961). "Recurrent Hypoglycemia and Retroperitoneal Fibrosarcoma"

Steinke, J., Soeldner, S., and Renold, A. E. J. Clin. Invest. (abstract) 41:1403 (1962) "Insulin-like activity of extracts from large sarcomatous tumors associated with hypoglycemia"

Volk, B. W., Goldner, M. G., and Wainfeld, B., Geriatrics, 15:473-479 (1960). "Spontaneous Hypoglycemia with Abdominal Spindle-cell Sarcoma"

Whitney, J. E., and Heller, B. I., Am. J. Med., 30:633-636 (1961)

Whitney, J. E., and Massey, C. G., J. Clin. Endocrinol. 21:541-547 (1961).

B. Adrenal Cortical Carcinomas:

Anderson, H. B., Am. J. Med. Sci., 180:71-79 (1930) "Tumor of Adrenal Gland with Fatal Hypoglycemia"

Aszkanazy, C. L., Jenkins, L., and Simpson, W. W., Can. Med. Assoc. J. 79:482-484 (1958) "Adrenal cortical carcinoma associated with hypoglycemia"

Broster, L. R., and Patterson, J., Brit. Med. J. 1:781-782 (1948) "An Unusual Case of Adrenal Carcinoma "

Huhnlein, E., and Meythaler, M., Arztl. Forsch., 12:189-204 (1958).

Lawrence, C. H., Ann. Internal Med., 11:936-948 (1937). "Adrenal Cortical Tumor: A report of four cases"

Thannhauser, S. J., J. Clin. Endoc. 9:791 (1949) Very short letter to the editor only- "Hypoglycemia in the Early Phase of Adrenocortical Carcinoma"

Dohan, F. C., et al J. Clin. Endoc., 13:415 (1953) "Increased Urinary Estrogen Excretion Associated with Adrenal Tumors: Report of four cases".

Schamaun, et al Schweiz Med Wschr. 87:1348, (1957).

Boss, J. H., Schweiz, Z., Allg. Path. 42:232, (1959) "Spontaneous Hypoglycemia as a Result of a Non-insulin-producing Tumor of the Adrenal Region"

Williams, R. et al "Hypoglycemia and abnormal steroid metabolism in adrenal tumors" Quart. J. Med., New Series XXX-269 (1961)

Eymontt, M. J., et al. "Cushing's syndrome with hypoglycemia caused by adrenocortical carcinoma" J. Clin. Endoc. & Metab. 25:46 (1965).

IV. Case Reports of Hypoglycemia Associated with Endodermal Tumours.

A. Hepatomas:

Beers, D. N., and Morton, J. J., Am. J. Cancer 24:51-55 (1935) "Primary Carcinoma of Liver with Hypoglycemia"

Crawford, W. H., Am. J. Med. Sci., 181:495, (1931) "Hypoglycemia in a Case of Primary Carcinoma of the Liver"

Gold, G. L., and Shnider, B. I., Ann. Internal Med. 51:890 (1959) "Some Unusual Syndromes Associated with Neoplastic Disease"

McFadzean, A.J.S., and Yeung, T. T., Arch. Internal Med. 98:720-731 (1956) "Hypoglycemia in Primary Carcinoma of the Liver"

Nadler, W. H., and Wolfer, J. A., Arch. Internal Med. 44:700-710 (1929) "Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma"

Schonfeld, A., Babbott, D., and Ganderson, K. N. Eng. J. Med. 265:231, (1961) "Hypoglycemia and Polycythemia Associated with Primary Hepatoma"

Thompson, C. M., and Hilferty D. J., Gastroenterology 20:158-165 (1952) "Primary Carcinoma of the Liver (Cholangioma) with Hypoglycemia Convulsions"

B. Gastric Carcinomas

Field, J. B., Keen, H., Johnson, P., and Herring, B., J. Clin. Endocrinol. 23:1229-1236 (1963) "Insulin-like Activity of Nonpancreatic Tumors Associated with Hypoglycemia"

Gonzalez, G., Gold, G. L., and Shnider, B. I., Ann. Internal Med., 58:149-154 (1963) "Gastrointestinal Carcinoma and Concomitant Hypoglycemia"

Goldner, M. G., Bull. N. Y. Acad. Med., 37:74-75 (1961) "Extrapancreatic tumors Associated with Hypoglycemia - Discussion by M. G. Goldner"

C. Colon Carcinomas

Floyd, J. C., Power, L., Rull, J., Fajans, S. S., and Conn, J., Clin. Res. 11:297 (1963) "Insulin and ILA in tissue Extracts and Plasma of Patients with Non-Pancreatic tumours associated with Hypoglycemia"

Tranquada, R. E., Bender, A. B., and Beigelman, P. M., New Eng J. Med. 266:1302-1306 (1962) "Hypoglycemia Associated with Carcinoma of the Cecum and Syndrome of Testicular Feminization"

V. References Pertaining to Mechanisms of Hypoglycemia

Ashmore, J., Wagle, S. R., and Uete, T., Advances in Enzyme Regulation, 2:101, (1964) Pergamon Press " Studies on Gluconeogenesis"

Bauer, J. M., and Wu, C., Cancer Res., 20:848 (1960) "A Study of Free Amino Acids and of Glutamine Synthesis in Tumor-bearing Rats"

Buse, M. G., Buse, J., McMaster, J. and Krech, L. H., Metabolism 13:339 (1964) "The Effects of Tris (Hydroxymethyl) Aminomethane (THAM) on Glucose Utilization of Skeletal Muscle

Cahill, G. F., Advances in Enzyme Regulation 2:137 (1964) Pergamon Press. "Some observations on Hypoglycemia in Man"

Cahill, G. F., Jr., Ashmore, J., Renold, A. E., and Hastings, A. B., Am. J. Med. 264: (1959) "Blood Glucose and the Liver"

Combes, B., and Schenker, S., Personal Communication.

Dole, V. P., J. Biol.Chem, 237:2758 (1962) " Insulin-like actions of RNA, adenylic acid, and adenosine"

Eisenberg, S., Personal Communication.

Elrick, H., Hlad, C. J., and Arai, V., Metabolism 11:46 (1962) "Influence of Certain Nucleosides on Glucose Utilization in Man"

Horecker, B. L., and Hiatt, H. H., New Eng J. Med, 268:177 (1958) "Pathways of Carbohydrate Metabolism in Normal and Neoplastic Cells"

Ingle, D. J., Diabetes 14:93 (1965), "Comparison of Pancreatic and Steroid Diabetes in respect to Tumor Growth and Glycosuria"

Karsh, R. S., Freedman, H., and Blumenthal, H. T., Amer. J. Med., 30:619 (1961) "Functioning Islet Cell Carcinoma Metastasizing as Spindle Cell Tumor"

Kipnis, D., Personal Communication.

Landau, J., Wynn, V., Cooke, J.N.C., and Kennedy, A., Metabolism 502 (1962) "Effects of Anabolic Steroid Methandienone on Carbohydrate Metabolism in Man"

Lardy, H. A., Foster, D. O., Shrago, E., Ray, P. D., Advances in Enzyme Regulation 2:39 (1964) Pergamon Press "Metabolic and Hormonal Regulation of Phosphopyruvate Synthesis"

Lehninger, A. L., Harvey Lect. 49:176 (1955) "Oxidative Phosphorylation"

Luft, R., Ikkos, D., Palmieri, G., Ernster L., and Ofzelius, B., J. Clin. Invest. 41: 1776 (1962) " A Case of Severe Hyper-Metabolism of Nonthyroid Origin with a Defect in the Maintenance of Mitochondrial Respiratory Control: A Correlated Clinical, Biochemical, and Morphological Study."

Madison, L. L., Mebane, D., Unger, R. H., and Lochner, A., J. Clin. Invest. 43:408 (1964) "The Hypoglycemic Action of Ketones. II. Evidence for a Stimulatory Feedback on the Pancreatic Beta Cells"

Marks, P. A., and Bishop, J. S., J. Clin. Invest., 36:254 (1957) "The Glucose Metabolism of Patients with Malignant Disease and of Normal Subjects as Studied by means of an Intravenous Glucose Tolerance Test"

Passonneau, J. V., and Lowry, O. H. Advances in Enzyme Regulation 2:265, (1964) Pergamon Press. " The Role of Phosphofructokinase in Metabolic Regulation"

Reichard, G. A., Jr., Moury, N. F., Hochella, N. J., Patterson, A. L., and Weinhouse, S., J. Biol Chem. 238: 495 (1963) "Quantitative Estimation of the Cori Cycle in the Human"

Roffs, A. H., and Correa, A. H., J. of Cancer Res. 11:126 (1927).

Samols, L., Postgrad. Med. J., 39:634 (1963) "Hypoglycemia in Neoplasia"

Sharma, C., Manjeshwar, R., Weinhouse, S., Advances in Enzyme Regulation 2:189 (1964) Pergamon Press, "Hormonal and Dietary Regulation of Hepatic Glucokinase"

Silverstein, M. N., Wakim, K. G., Bahn, R. C., and Bayrd, E. D., Proc. Soc.Exp. Biol. and Med. " A Hypoglycemic Factor in Leukemic Tumors"

Silverstein, M. N., Wakim, K. C., Bahn, R. C., Bayrd, E. D. Proc. Mayo Clinic Additional Preliminary Observations on the Hypoglycemic Factor

Sols, A., Salas, M., and Vinuela, E., Advances in Enzyme Regulation 2:177 (1964) Pergamon Press "Induced Biosynthesis of Liver Glucokinase"

Terpeka, A. R., and Waterhouse, C., Amer. J. Med.20:225 (1956) "Metabolic Observations during the Forced Feeding of Patients with Cancer"

Warburg, O., London: Constable, 1930 " The Metabolism of Tumors"

Weber, G., Henry, M. C., Wagle, S. R., and Wagle, D. J., Advances in Enzyme Regulation 2:335, (1964) Pergamon Press. "Correlation of Enzyme Activities and Metabolic Pathways with Growth Rate of Hepatomas"

Weber, G., Singhal, R. L., Stamm, N. B., Fisher, E. A., Mentendiek, M. A., Advances in Enzyme Regulation, 2:1 (1964) Pergamon Press. "Regulation of Enzymes Involved in Gluconeogenesis"

Weinhouse, S., Advances in Cancer Res. 3:269 (1955) "Oxidative Metabolism of Neoplastic Tissues"