Bulletin of

Staff Meeting

Minnesota General Hospital
University of Minnesota

Spontaneous Hypoglycemia

VOL. V THURSDAY, OCTOBER 5, 1933 NO. 1

INDEX

I. GROUP CONSCIOUSNESS.

"The purposes of Staff Conferences, according to Parnall and Clough, are: (1) stimulate the best in scientific medicine; (2) develop group consciousness; (3) promote cooperation; (4) provide post-graduate education; (5) check incompetency, ignorance and carelessness; (6) promote securing of autopsies; (7) prevent unnecessary surgery; (8) check infections, consultations and end-results of treatment; (9) periodically appraise experience and review critically work of all departments; (10) inaugurate preventive measures against infections and complications.

The program should consist of: (1) selected cases containing object lessons in improvement of technique of diagnosis or therapy; (2) group studies of various common diseases and injuries with special reference to end-results; (3) discussion of special reports from various clinical and scientific departments; (4) discussion of ways and means of elevating scientific efficiency of hospital and medical staff." The preceding remarks are requoted from The Bulletin, Staff Meeting U. of M. IV: Oct. 3,'32. They were made by Oschner, A.: Bull. Amer. Coll. of Surg. XVI: 17-19, (June) '32.

Today marks the beginning of the fifth year of the present series of Staff Meetings (144th Meeting). These meetings are held weekly during the regular school year in spite of the fact that practically every department carries on intense intra-departmental activities. As we look over the various objectives of Staff Conferences, it appears that the majority can be met by departmental meetings. Exceptions are notes, however, in Par. 1: (2) develop group consciousness, (3) promote cooperation, and (9) periodically appraise experience and review critically work of all departments. Our program in the past has probably covered all points except Par. 2: (3) discussion of special reports from various clinical and scientific departments. This year special arrangements are being made whereby each department will be given the opportunity to present its activities. These reports will consist chiefly of clinical problems, and will give the entire group an opportunity to learn what is going on. We are pleased to announce that Dr. Leo G. Rigler and associates have promised to take over an early meeting in October for this purpose and several other departments have expressed their willingness to come in on the scheme. This is a blanket invitation to all to provide as a starter one program per department.

We hope during the coming year to have many distinguished guests. If you will cooperate with us by letting us know in advance of anyone who will be in town at the time of our meeting, we would be most glad to arrange for their appearance on our program. It must be remembered that a good hospital staff meeting is not a medical society meeting - not a clinical-pathological conference. It is not the purpose of such meetings to turn over the time for formal papers by outside speakers. It is essentially our own meeting and can be made a success in this way.

As in the past, the Citizen's Aid Society will sponsor the publication of The Bulletin. We are asking each department to supply us in advance with abstracts of the material to be presented at their meeting. In this way, a complete set will be developed. We know you will be pleased with the new meeting quarters which are adequate for the first time. We hope that you will enter into the spirit of the occasion, as you have done in the past, and we bespeak your cooperation. Especially do we appreciate any criticisms or suggestions for improvement of the meetings. We are fortunate in having Dr. Rudolph Koucky with us again this year as his ability to prepare clinical pathological correlations is too well known to need commend.

Special arrangements are being made to take care of calls during meetings. The time, 12:15 to 1:15, is a compromise for the group and the limits will be rigidly enforced. When you have received your lunch, come inside and sit down and take an active part in the

meetings. With your cooperation the meetings are bound to be a success. Thank you!

II. MORTALITY REPORT.

Malignant:

1. Examined:

Carcinoma, bladder	m65
Carcinoma, cervix	f62
Carcinoma, lung	m40
Carcinoma, pancreas	m71
Carcinoma, stomach	m58
Carcinoma, stomach	m61
Carcinoma, stomach	m62
Carcinoma, stomach	f64
Carcinoma, tongue	m59
Carcinoma, vulva	f59
Hodgkin's Disease	m56
Mediastinal tumor, probably sarcoma	m21

2. Not Examined:

Brain tumor	f14
Brain tumor	f 4
Carcinoma, mouth	m67
Carcinoma, ovary	f67
Carcinoma, stomach	f57
Carcinoma, stomach	m70

Non-Malignant:

1. Examined:

Abscess, lung	m41
Anemia, pernicious	f46
Anomalies, congenital multiple	m1da
Appendicitis, acute, pelvic abscess	f23
Appendicitis, ruptured	m35
Appendicitis, ruptured, with peritonitis	f 5
Arteriosclerosis, gangrene, leg	m60
Arteriosclerosis, gangrene, leg	m65
Bronchopneumonia, bilateral	f3mo
Bronchopneumonia, fracture of femur	m47
Diabetes Mellitus, gas gangrene	m52
Diabetes Mellitus, acute pancreatitis	f77
Emphysema	m2
Endocarditis, bacterial subacute	f76
Enteritis, acute	f3mo.
Erysipelas	m20da
Fistula, rectovaginal	f15mo
Fracture, cervical spine	m19
Fracture, cervical spine	m16
Glomerulo-nephritis	m2
Glomerulo-nephritis	f53
Heart Disease, congenital	m11da
Heart Disease, rheumatic	m12
Hemorrhage, intracranial	f2hr.
Hypertension	m43
Hypertension	m47
Hypertension	m59
Hypertension, uremia	f42
Hypertrophy, prostate	m72
Hypertrophy, prostate	m75
Hypertrophy, prostate	m66
Hypertrophy, prostate	m80
Kidney stone	m33
Kidney stone, bilateral	m45
Leukemia, acute	m1mo
Mastoiditis, acute	f6
Obstruction, intestinal, peritonitis	m18
Osteomyelitis, acute	m7mo.
Pemphigus, neonatorum	m16da.
Perforation, esophagus	m47
Peritonitis, (appendicitis - operated elsewhere)	f18
Pertussis, bronchopneumonia	m1
Pneumococci septicemia from mastoid	f36
Pneumonia pneumococcus	m
Premature	m2hrs
Premature	f2hrs
Premature	f12hrs
Pulmonary embolus, anterior poliomyelitis	m24
Rupture, spleen, accident, coroner's case	f49
Stillborn	m o
Stillborn	m o
Stillborn	f o
Stillborn	f o
Stillborn	f o

Syphilis, Possible brain tumor	m63
Tuberculosis, adrenals	m42
Tuberculosis, peripheral neuritis	f29
Ulcer, duodenal perforated	f39

2. Not Examined:

Abscess, pulmonary	m47
Appendicitis, acute	f33
Appendicitis, acute	f42
Arteriosclerosis, cerebral	m66
Arteriosclerosis, cerebral	m71
Empyema, encapsulated, ca. prostate?	m62
Hypertension	m54
Hypertrophy, prostate	m75
Pansinusitis, brain abscess	f22
Peri-rectal simuses and fistulae, multiple	m51
Pneumonia, lobar	m ½
Premature	f24da
Premature, otitis media	m16da
Spastic ileus	f-
Stillborn	m o
Thrombosis, coronary	f54
Ulcer, duodenal	m -
Not diagnosed	m75

	Deaths	Autopsies	%
Apr.May June '33	94	69	73.4
Apr.May June '32	98	68	69.4
Jan.Feb.Mar. '33	119	89	76.
Jan.-June '33	213	158	74.1
Jan.-June '32	179	133	74.3

III. CASE REPORT:

FUNCTIONAL NEUROSIS (Pancreatic adenoma). Path. Rudolph Koucky.

Case is white male, 45 years old, admitted to Minnesota General Hospital 1-21-31, discharged 3-4-31 (42 days).

Injuries

1927 - While working at coal dock, a piece of coal, size of an apple, hit patient on top of head. He dropped to floor, apparently unconscious.

1928 - Sustained injury to testicle followed by great deal of swelling. Job required working in underground passage where he constantly bumped his head on the ceiling. Patient felt that these injuries contributed to his subsequent illness. From time of accident, had constant ache over the vertex of head (did not radiate). Through remainder of 1927 (at about monthly intervals) had attacks of dizziness which lasted as long as 24 hours - not accompanied by nausea or vomiting.

Spells

1929 & 1930 - Continued to have attacks of dizziness. Fainting spells developed. Became weak during attacks and occasionally had to stop work for periods of 2 to 3 days. On one occasion, was found unconscious and had to be taken home in a car. Loss of memory over 24 hours. In intervals between attacks, continued to work.

Past History

Not significant.

Family History

Not significant.

Admitted

1-21-31. Physical examination: Head and neck - normal. Lungs - normal. Heart - normal blood pressure 110/50, Abdomen - normal. Neurological - cranial nerves normal, sensorium normal; superficial reflexes 1+ increase; motor system normal; examination essentially negative. Laboratory: Urine (6 examinations)- trace of albumin (one occasion), few leucocytes few occasions (uncatheterized). Blood - Hb. 92%, wbc. 6,200, Pmn's 63%, L 30%, M 6%, E 1%. Blood, Wassermann - negative. Spinal puncture - fluid clear and colorless, pressure 130, jugular pressure 255, 2 cells, protein test negative, serology negative. X-ray of skull - negative. Staff note: History consists of attacks, lasting up to 24 hours, characterized by dizziness, weakness and

on some occasions by unconsciousness. Ascribes these attacks to various injuries. Also gives history of having tapeworm infestation. The physical examination and other data is essentially negative.

Attack related to hunger

2-1-31 - In 12 days since admission, patient has had uneventful progress. Complained of headaches nearly every day and occasionally of vague discomfort. 6:05 A.M. - Suddenly developed "an attack". (Following description of "the attack" was written by intern.) "Patient seems drowsy, responds slowly and inadequately. There is coarse twitching of left side of face. Little finger of left hand is jerking regularly. There is resistance when one attempts to move his arm. 11:30 A.M. - He volunteers the fact that a glass of milk makes him better at once. Nurse said he was given a glass of milk and improved immediately. Patient's impression is that hunger brings on the attacks. Never has them after eating. First had attacks at 11 A.M. but for past 4 years, attacks are usually between 5 and 6 A.M."

2-2-31 - 6:30 A.M. - Complains of slight headache. Asks for milk and feels better.

Attacks continue

2-3-31 - 7:30 A.M. - Found in bed with eyes half open. Was spoken to but did not respond. Pulled covers over face. When covers were removed, he struck at the attendant. Patient was relaxes when first seen, but later became tense. 8:30 A.M. - Given cup of milk. 10 A.M.- Perspiring. Slept for one hour. 11 A.M.- Face flushed. Rather stuporous. 12:30 P.M. - After dinner (?), patient got up, went to the bathroom. Appeared much better. Says he does not remember what happened in the morning.

2-6-31 - 7:40 A.M. - Hands twitching. Only responded by shaking head. Would not take breakfast or milk. Threw himself on bed and was very tense. 8:10 A.M. - Less rigid. Perspiring profusely. Very drowsy. States that he is sick. 12:45 P.M. - Got up after being in bed all morning, went to bathroom; states he does not remember what happened in morning.

2-8-31 - 7:15 A.M. - Patient kicking, throwing arms about, etc. Will not talk or attempt to control himself. Attack lasted 15 minutes. Began to perspire profusely and again covered his head with bed clothes. Will open eyes when spoken to but not talk. 9 A.M. - Took glass of milk. 10:30 A.M. - Up and about.

2-9-31 - 7:30 A.M. - Nurse went into room with breakfast. He asked what meal consisted of. When told he had better eat, he failed to respond further. Pulled covers over his head and refused to eat. Remained in stuporous state all morning. Refused dinner. Would not answer questions. Only responds by opening eyes when spoken to. 12:45 P.M.- Began to kick violently and strike wall, bedside stand, nurse, etc. Put in restraints. Hangs head over side of bed, cries, moans and will not respond. 6 P.M. - Patient asks why he is in restraints. 8 P.M. - Asks for glass of milk. 8:30 P.M. - Got up out of bed, went to bathroom. 11:45 P.M. - Says he fells fine. Asked for glass of milk.

2-10-33 - 6:50 A.M. - Same attack repeated. 7:15 A.M. - Very violent. (No further description).

2-12-33 - Another attack similar, beginning at 6:05 A.M. (No description).

3-4-31 - In interval since last attack, has had no seizures. Generally felt very well except for headaches from time to time. Has been irritable. Has not shown any of the manifestations of the attacks previously described. Discharged.

Clinical Impression: Functional neurosis.

Note: The above progress notes have been taken almost without any shortening or change from the intern's and nurse's notes.

Subsequent course: After leaving the hospital, patient at a later date went to another clinic. Diagnosis of adenoma of the Islands of Langerhan's was made. Pancreas explored. A 3 cm. tumor was excised from the tail of the pancreas. 1933 - The case is cited in the report by Judd as a permanent cure.

IV. CASE REPORT:

RUPTURED GASTRIC ULCER: MALIGNANT TUMOR OF PANCREAS.

(Origin in Islands of Langerhan's?).

Path. Rudolph Koucky.

Case is that of a white female, 40 years of age, admitted to Minnesota General Hospital 4-13-33, expired 4-18-33 (5 days).

Ulcer history

1931 - Epigastric pain. Varied in character from burning sensation and dull ache to sharp cramplike pain. Occurs at varying intervals after meals. Very definite food relief.

11- -32 - Severe attack of pain.

Poor response to medical treatment

1- -33 - Admitted to another hospital. Given modified Sippy diet. Remained for one month. X-ray showed "ulcer of stomach." Two weeks after leaving hospital, pain recurred and to increase in severity. Attacks mostly at night. Vomiting relieved pain.

Perforation

4-12-33 - Came to Minneapolis to visit Out-Patient Department next day. About 3 A.M., while at hotel, had very severe pain in epigastrium followed by localization in right lower quadrant. Given hypodermic injection.

Operation

4-13-33 - 8 A.M. (5 hours later). Admitted. Physical examination: Extremely ill. Extremities cold. Obviously suffering severe abdominal pain. Pulse 140. Breath has foul odor. Chest - normal. Heart - normal. Abdomen - slightly distended, generalized rigidity, diffuse tenderness with marked rebound tenderness throughout. Clinical impression: Perforated peptic ulcer with peritonitis. Taken to operating room immediately. Perforated gastric ulcer found on lesser curvature of stomach just proximal to pylorus in close proximity to gall-bladder. Perforation closed. Laboratory: Urine - slight cloud of albumin, numerous white blood cells (few clumps). Hemoglobin - 104%. Blood leucocytes 9,800. Neutrophiles 93%. Cultures from abdomen (at time of operation) - gram + coccus, probably staphylococcus. 4 P.M. - Blood pressure 92/78. Feels very weak.

Restless, Transfusion

4-14-33 - Considerable mucus in throat. Blood Pressure 110 (sys) 5:30 P.M. - Blood Pressure 60/50. 9 P.M. - transfusion of 500 cc. citrated blood. 10 P.M. - Very restless.

Hunger - Hypotension (Note)

4-15-33 - Blood Pressure 80/60. 2 A.M. - Hunger sensations. Blood Pressure 90/60. Pulse 132. 6 A.M. - Complains of stiffness of legs. 12 noon - Talks irrationally throughout day. X-ray of chest shows bronchopneumonia, right base (with fluid). Temperature 103.4, Pulse 130. Respirations R 22. More rational.

Stupor, Muscle Twitchings, Restlessness. (Note)

4-16-33 - Stuporous. Twitchings of face and extremities. Very cyanotic and irrational. Material draining from abdominal wound is bile-stained. Very noisy and restless.

4-17-33 - Still restless and noisy. Placed in oxygen tent because of bronchopneumonia.

Muscle twitching persists. Exitus. (Note

4-18-33 - Temperature 104.2. Pulse 124. Respirations 24. Condition worse. Cyanosis more marked. Slight edema of extremities. Muscular twitchings. 8 P.M. - Temperature 106.4. 8:05 P.M. - Expired.

Note: In view of possible hypoglycemia these clinical notes are of interest and may be significant (?) But the picture is complicated by the gastric accident.

Well-Nourished

AUTOPSY: The body is a well-developed and nourished, white female about 40 years of age, measuring 168 cm. in length and weighing approximately 120 lbs. Rigor, edema, cyanosis and jaundice are absent. Hypostasis is slight, purplish and posterior. There is a recent 16 cm. sutured operation wound in the left upper

quadrant which is draining bile. There is an old scar in the midline below the umbilicus (well healed). Each pupil measures 4 mm. in diameter. Subcutaneous fat is abundant.

Localized peritonitis.

Peritoneal Cavity: The large omentum is attached in the pelvis, separating the peritoneal cavity into 2 large divisions. The anterior division is filled with bile-stained exudate. This is most marked about the liver where the exudate is greenish and gelatinous. The posterior cavity, containing all the bowel, is free of exudate. The Appendix is absent.

Pleural Cavities: are free of fluid. No adhesions. The Pericardial Sac is smooth and glistening. Heart weighs 240 grams. Musculature is of good consistence. No fibrosis, infarcts or softening. Mural endocardimum and valves are smooth and clean. Root of the Aorta is of good size and is smooth. Coronaries are large and soft.

Bronchopneumonia.

Right Lung weighs 460 grams, Left 750 grams. Left lower lobe shows extensive collapse. This collapsed area is diffusely infiltrated with pneumonic areas. Right lung shows non-infected collapse of moderate degree in lower lobe.

Spleen weighs 150 grams, is soft and red. The follicles are prominent.

Metastatic tumor.

Liver weighs 1700 grams, is yellowish and soft and appears somewhat swollen. In center of liver, there is a firm white non-encapsulated nodule about 1 cm. in diameter. It is composed of typical malignant tissue.

Necrosis of gall-bladder.

Gall-Bladder is thick and edematous. Just above cystic duct, there is a necrotic area which has perforated. This perforation is about 1.5 cm. in length and lies directly over the peptic ulcer.

Ulcer (Open).

Gastro-Intestinal Tract: The esophagus shows postmortem change. Stomach is small and contains some mucus. Pylorus and first part of duodenum is hard and fibrous. Exact position of end of pylorus cannot be determined because of fibrosis. In this hard area there is a perforated ulcer, measuring approximately 1.0 cm. in diameter. Its edges are hard and the ulcer is open. There are no signs of sutures at this time. Small bowel is adherent in pelvis over a small area. Colon shows no change.

Tumor.

Pancreas: is large, feels firm, and has a normal color. There is no evidence of pancreatitis or fat necrosis. Ducts are not dilated. No tumors, cysts, fibrosis or inflammatory changes in head or body. There is a round tumor situated in the extreme tip of pancreas, which measures 5.5 cm. in diameter. The tumor is well encapsulated and the fibrous capsule measures 4.0 mm. at its thickest part. It appears that it could be enucleated from the body of the pancreas quite easily. It has not infiltrated into the adjacent structures. At one point, a small tag of mesentery is attached to its surface; it can be stripped away easily. On the anterior and inferior surface of this tumor, there is lobule which measures about $1\frac{3}{4}$ cm. in diameter and 1.5 cm. in breadth which seems to be a direct outgrowth from the original tumor. This second tumor, however, has no definite capsule and it feels cystic. On cross section, it is made up of a very red, soft, fleshy material. The first tumor is quite firm, yellowish and appears glandular. The pancreas superior to the main tumor contains an encapsulated nodule about 1.0 cm. in diameter which is white and can be easily shelled out from its bed. Within the body of the main tumor, there are 2 small cysts measuring about 4 mm. in diameter.

Adrenals: are plump, well formed, and show no hemorrhage or degeneration. No tumor.

Right Kidney: weighs 175 grams, Left 150 grams. Capsule strips easily on both sides and leaves a smooth surface. Kidneys do not cut with increased resistance. The pelvic fat is not increased in amount.

Bladder: is not trabeculated. No diverticulae, tumors or cystitis.

Salpingectomy.

Genital Organs: Uterus is enlarged. Both tubes and right ovary are absent. Left ovary contains large corpus luteum. Considerable fibrosis and old adhesions at site of bilateral salpingectomy. Interior of uterus is smooth and contains a small amount of blood.

Aorta: shows no atheromatous change. No appreciable enlargement of Lymph Nodes. No evidence of malignant invasion of any lymph nodes.

Organs of Head and Neck: Not examined.

Gross Diagnosis:

1. Ruptured gastric ulcer.
2. Acute localized peritonitis.
3. Right pulmonary atelectasis.
4. Left infected atelectasis (bronchopneumonia).
5. Old bilateral salpingectomy, right ovarectomy.
6. Old appendectomy.
7. Recent operative closure of gastric ulcer (clinical).
8. Tumor of pancreas (malignant); type, Islets of Langerhans?
9. Metastatic tumor in liver.
10. Necrosis and perforation of gall-bladder.

Cultures:

Abdominal fluid - scanty growth of streptococci; not hemolytic; forms very short chains.

Blood Sugar:

A specimen of blood taken from the right femoral vein was examined for blood sugar. The examination was begun at 11:05 P.M., exactly 3 hours after death. The readings were checked four times and checked with each other. The calculated blood sugar was 14.7 mg. per 100 cc. (extremely low).

Microscopic Examination of Tumor:

A moderate amount of necrosis is present. The stroma is light supporting tissue and is quite vascular. The tumor cells have a uniform appearance. They are large, cuboidal or oval and have a distinct cell membrane. The cytoplasm is abundant and finely granular. The nuclei are central, small and hyperchromatic. The general arrangement is wide branching cords separated by loose stroma. No papillary, acinar, squamous or scirrhous structure is found.

The appearance is quite different from any tumor of the parenchymal organs. It suggests to some extent the cellular forms of endotheliomata.

Benseley Stains:

A fine dust-like granulation is present in the cytoplasm. This is not typical of the normal pancreatic islet cell but does conform very well with the granules described in cells of tumors of the islets.

Other Differential Stains:

Give no further information.

Conclusion:

Carcinoma of pancreatic islets.

Letter from Referring Physician:

In response to a questionnaire, doctor states that he had never observed any attacks suggesting hypoglycemia. No blood sugar estimations. Husband knows of no unusual circumstances in wife's history suggesting hypoglycemia.

V. ABSTRACT:

SPONTANEOUS HYPOGLYCEMIA.

Abstr.
Rudolph Koucky.

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History:

Recognition of spontaneous hypoglycemia developed in an interesting manner. At first such a state was considered theoretically possible; then the syndrome was described clinically without anatomical proof; and finally the clinical picture, anatomic and physiologic basis were all demonstrated in the same patient.

1902 - Nicholls: described 3 x 2.5 mm. adenoma of islands. No mention of hypoglycemia.

1922 - John: Artificial hypoglycemia after insulin injection.

1924 - Harris: devised the term "hyperinsulinism" and described the clinical picture.

1927 - Wilder, Allan, Powers, Robertson: demonstrated a carcinoma of the Islands of Langerhans with hypoglycemia.

1928 - Finney and Finney: Case of hypoglycemia without demonstrable tumor. Resected tail of pancreas without appreciable benefit.

1929 - McClenahan and Norris: Hypoglycemia and adenoma of pancreas.

1929 - Howland, Campbell, Malthy and Robinson: removed adenoma with relief of the hypoglycemia.

1929-1933 - Several cases have been reported. In addition to the typical picture of spontaneous hypoglycemia associated with a secreting tumor of the pancreatic islands, other phases have been brought out:

(1) hypoglycemia without disease of the pancreas.
(2) hypoglycemia with tumors of pancreas but without relief after resection.
(3) tumors of pancreatic islands without hypoglycemia.
(4) hypoglycemia with disease of other organs and no disease of pancreas.

Anatomy of Pancreatic Islands:

R. R. Bensley has studied the pancreas for many years. In addition to contributions regarding the normal islands, he has also guided the anatomic studies on the tumors of these structures.

The islets vary greatly in size and number. The upper limit of size is estimated as 3 mm. The number varies in the individual and specie. In the guinea pig, it is said that there are 22.3 islands per cmm. In man, the average number is around 12. There is an excess of approximately nine times the necessary number of islets. They are most numerous in the splenic portion of the gland. The cells do not form a syncitium but on the other hand are easily torn apart. The nuclei are large, vesicular and have a nucleolus. The cytoplasm contains numerous granules which morphologically and chemically can be differentiated into two types called "alpha" and "beta". Each cell contains only one type of granule. The beta cells are thought to be associated with insulin production. Cells of islet origin can be readily distinguished from pancreatic acini by 1 - 10,000 aqueous (normal saline) solution of neutral red. Islet cells take on a yellow-red and acinar cells a rose color. Fresh unfixed (not frozen) tissue is used. There is no increase of islands after inanition or after secretory exhaustion. The islets are not isolated from the rest of the gland. They are connected or directly continuous with the duct system by ramifying and tortuous tubules. Genetically, they are derived from the same tissue as acini but the adult structures are not reversible and cannot be transformed one to the other. New islands apparently can be formed.

Pathology:

Tumors of the islands of Langerhans may be divided on a physiological basis into the following:

1. Functioning (secreting insulin) tumors.
   a. Carcinoma without metastasis.
   b. Carcinoma with metastasis.
   c. Adenoma.

2. Non-functioning.
   a. Adenoma (single or multiple).

Cysts of the islets and non-functioning carcinomas have not been described. The distinction between adenoma and carcinoma without metastasis is very indefinite (non-encapsulation, infiltration).

The tumors present the usual characteristics of adenoma or carcinoma. The color usually is either yellowish or red. The adenomas are encapsulated. The position is usually in the tail but may occur elsewhere in the gland. The size tends to be small, many have been very small. This is more true of the non-functioning adenomas. Shields Warren collected 20 such cases and in many the adenomas were microscopic in size. These non-functioning tumors may be multiple.

The microscopic picture in general is typical of adenomas or carcinomas elsewhere. The minute cytology of the tumor is considered to be significant. The nuclei retain the form of island cells and have a nucleolus. The cytoplasm tends toward the normal islet type but does not retain this form entirely. Alpha granules probably are not present. The beta granules react chemically like the normal. Morphologically, however, there is some variation. Irregular shreds and masses of the material may be present. In some cells, the granules are absent. In others, it has an irregular distribution. According to Bensley, the morphology of the tumor cytoplasm shows

a "reference" to the normal island. The reaction to neutral red persists and is very important in differentiating acinar from island tissue.

Associated Pathology (Terbruggen):

The effect of prolonged hypoglycemia on the other organs of the body apparently is not marked. There is a marked diminution of the glycogen content of all the tissues. Fat is very scanty in the parenchymal organs. The brain shows hyperemia and dilation of all the vessels. Atrophy ("Hirnatropie") is described. Fatty droplets in the ganglion cells and a perivascular leucocytic reaction have been seen. The changes appear to be reversible. The degenerative changes in the ganglion and glia cells observed after fatal insulin shock were not seen. A few hemorrhagic areas in brain and other organs were present. (Based on one case). Edema of the brain is not described.

Etiology of Hypoglycemia:

When the clinical syndrome was first described, hypoglycemia and hyperinsulinism were considered somewhat synonymous, and each was in direct quantitative relation to the other. The discovery of tumors of the islands of Langerhans and the improvement after their removal proved that in some cases at least this synonymous use of terms was correct. Here a relation between hypoglycemia and an excess of insulin-secreting tissue was clear. Rabinowitch, however, points out that there is normally a great excess (9X) of such tissue and that the tumors have usually been small. He suggests therefore that the secretion is perverted (like in exophthalmic goiter?) and has an abnormally high potency.

Not all adenomas of the islets produce hypoglycemia. Warren presents 20 such cases and makes no mention of hypoglycemia in connection with any. This is in 1926. In 1931, Margaret Smith reported 4 cases of adenoma found incidentally at autopsy. Of these, two had no symptoms (non-functioning), one had a classical history and one was found on subsequent questioning to have been a "mental defective" because he had periods of loss of memory. Therefore adenomas probably occur without hypoglycemia but in some of these cases the evidences of such attacks is found only on careful questioning and analysis.

To further confuse the relation of pancreatic adenomas to hypoglycemia are reports of "dysinsulinism" (Smith, Buchner, Love). These cases are diabetics (hyperglycemia) who have attacks of hypoglycemia and in some of these adenomas of the islands have been found.

Finally, hypoglycemic attacks, some fatal, can occur in the absence of demonstrable island adenomas or can occur in other diseases. H. Frank ('31) lists the causes of hypoglycemia as follows:

1. Tumors of pancreatic islands.
2. Addison's disease (clinical and experimental).
3. Hypophyseal disease.
4. Liver damage.
5. Lactation.
6. Status thymico-lymphaticus (?).
7. Progressive muscular atrophy.
8. Parkinson's disease.
9. Undernourishment.
10. Children of diabetic mothers.
11. Unknown cause.

In one case (Rabinovitch and Barden) the only lesions found at autopsy were small inflammatory lesions of the pancreas and a degenerative process in the adrenals which destroyed the medulla. Other cases are those of Tuttle (carcinoma of liver); Nadler and Wolfer (carcinoma of liver); Crawford, (Carcinoma of liver) and Anderson (tumor of adrenal). The degree of hypoglycemia may be marked in these cases without pancreatic tumors. In two, the blood sugar was between .02% and .00%. One was of unknown origin and the other was due to liver damage. Several reports are found of cases in which the diagnosis of pancreatic adenoma was made and exploration was done without finding the tumor. Resections of the tail of the pancreas in these cases have been of little benefit.

It would appear that the following conclusions can be drawn:

1. **Hypoglycemic attacks may be due to functioning tumors of the pancreatic islands.**
2. **Such tumors may exist in the diabetic and give rise to dysinsulinism (hyper and hypoinsulinism).**
3. **Such tumors may exist without hypoglycemia.**
4. **Hypoglycemia can be found associated with diseases or tumors of other organs.**

Clinical Features:

The subjective signs of the disorder are centered entirely about the hypoglycemia attacks. These are cyclic. They may occur at a given time each day or may be irregular in their appearance. They usually appear late after meals (before noon meal is common time) and are brought out or aggravated by physical and mental strain. They last from a few hours to as much as 36 hours. They are aborted by the intake of food--a fact frequently known by the patient.

The typical attack begins as a vague distress in the stomach with uneasiness or anxiety. Hunger and sleepiness next appear. The next stage apparently is variable. The patient may lose his memory but continue to go about his activity (very awkwardly); he may know what he is doing but has no voluntary control; or, he may become stuporous or unconscious. Motor incoordination seems to be very common. The next stage is that of stupor with neurological signs: twitchings, convulsions (very rarely with foaming at mouth or the biting of the tongue), cranial nerve paralysis, hemiplegia and positive Babinski. All these findings are variable and not constant. During the course, emotional changes are frequent. Perspiration is marked. Numbness of lips and back was observed in one case as a prodromal sign of the attack. Between these attacks the patients appear to be normal.

Blood sugar readings have been collected by Barnard:

Author	Sex	Age	Blood Sugar %	Lesion
Wilder	M	40	.03	Ca, metastasis
Thalheimer	F	57	.03	Ca, no metastasis
McClenohan	M	41	.04	Adenoma
Howland	F	52	.04	Ca, no metastasis
Carr	M	19	.04	Adenoma
Smith	M	40	.05	Adenoma
Terbruggen	F	30	.03	Adenomata
Barnard	F	40	.02	Adenoma

A 24-hour blood sugar curve is reported by Derick, etc.:

5 P.M.	--	Supper
6	34	
8	53	
10	24	faint, did not respond normally
12	55	
2 A.M.	64	
4	40	
6	42	
7:15		breakfast
8	33	
10	39	
12 noon	42	dinner
2 P.M.	74	
4	25	No complaints, appears normal

A similar study was made by Carr, etc.

A.M.	72	Normal
Dextrose given (155 gr. in 400 cc. water, including the juice of 3 oranges)		
30 min.	172	Patient active
60 "	183	" "
120 "	123	" "
180 "	80	Lethargic
240 "	56	Unresponsive
300 "	48	Stupor
360 "	42	Muscular twitchings

The sugar tolerance tests are stated to resemble those in the diabetic (?)

Derich:

	After 92 grams sugar orally.	95 grams intravenously
½ hr.	72	211
1	31	87
2	78	27
3	71	39

Carr:

Fasting 86
Dextrose (155 grams with juice of 3 oranges)

30 min.	122
60 "	152
120	125
150	110
240	57
300	53
360	52
420	57
480	51

The basal metabolic rate in the case reported by Derich, etc. was 28% "above the expected normal." This after removal of the adenoma dropped to +1%.

Diagnosis:

The typical case seems to be so characteristic that the diagnosis appears obvious. Nevertheless, the initial diagnosis in a large majority of cases was that of some neurological condition: neurasthenia, hysteria, mental disorder, epilepsy, brain tumor, etc. Frank states that every symptom present may be that of brain disease. The diagnosis is made from the blood sugar tests. It should be noted that some patients failed to show the attacks while in the hospital (under regular routine and rest). Strain, Fatigue, and irregular food intake bring on the attacks. In the interval, the blood sugar may be normal. The finding of hypoglycemia is not, of course, absolutely indicative of pancreatic tumor (under etiology).

Epilepsy, Narcolepsy, and Hyperinsulinism:

In line with the trend to consider epilepsy as a possible symptom of organic disease, Harris presented 3 cases of typical epilepsy and one of narcolepsy associated with hypoglycemia. The author cites several cases of grand mal symptoms induced by overdosage of insulin and points out that in the reported cases of spontaneous hypoglycemia neurologic signs including convulsions and coma are cardinal findings. Three cases of epilepsy reported by the author all showed the typical symptoms and blood sugar readings. Treatment by diet was satisfactory. One case of narcolepsy (sleep epilepsy) is reported to indicate that in some cases, narcolepsy is a manifestation of hypoglycemia. This patient improved after partial resection of the pancreas.

Treatment:

The number of cases encountered by any one group of physicians have been so small that no estimate of forms of treatment has been made. Apparently, two methods have been tried--diet and surgical removal of the tumor.

In one case (Carr, etc.), regulation of the patient by diet was attempted at first. In a short time, the diet failed to prevent attacks. The sugar tolerance tests showed a progression of the disease. Harris obtained relief by diet. In many cases, the history suggests that the patient had controlled the course fairly well by intake of food.

Holman ('33) reviewed the operated cases:

Date	Institution	Lesion	Result
1927	Mayo Clinic	Carcinoma with metastasis	Died
1928	Union Memorial, Baltimore	No lesion, tail resected	No significant improvement.
1928	Stanford Univ. Hospital	" "	Improved, not cured.
1929	Mayo Clinic	" "	No significant improvement

Date	Institution	Lesion	Result
1929	Mayo Clinic	No tumor, tail resected	No significant improvement
1929	Toronto Gen. Hospital	Adenoma	Cure
1931	Barnes Hospital, St. Louis	Adenoma	Cure
1931	"	"	"

There probably are other cases. Harris reports an additional case. The Mayo Clinic group includes 8 cases:

Time	Pancreas	Operation	Result
1926	Ca	None	Died
1928	No tumor	Excision tail	Better 1 year, now worse
1929	" "	" "	No improvement
1931	" "	" "	" " Reoperated Apr. 1933
1931	Chr. Inflammation	Split capsule	No improvement, better on diet
1931	3 cm. tumor	Removal	Cure
1931	2 small tumors	"	"
1932	No tumor	Exploration previously; excision of tail	No change No improvement

To date the resections of the tail of the pancreas have been unsuccessful. Holman, Judd, Harris and others recommend removal of larger portions. The operation does not carry a very great mortality.

In the case reported by Derich, etc. after resection of a tumor, the blood sugar (A.M. specimen) over a two week period ranged as follows: 176, 253, 156, 142, 200, 155, 152, 132, 136, 118, 148, 130, 140, 148, 152, 129, 94. During a 24 hour period (meals eaten), the lowest reading was 119 and the highest 165. The sugar tolerance test was as follows:

8	A.M.	115
8:20		25 gm. glucose
8:50		150
9:20		176
10:20		132
11:20		132

(Compare to preoperative readings recorded above).

Summary:

1. Adenomas of pancreas were observed as early as 1902 but the association with hypoglycemia was not demonstrated until 1927.

2. The first cure by excision of the tumor was in 1929.

3. The anatomy of pancreatic islets has been extensively studied by Bensley. Of practical interest are the specific staining reactions of insular tissue.

4. The tumors of pancreatic islands may be classified into functioning and non-functioning adenomas or carcinomas. It is possible that had the "non-functioning" types been studied more intensively some evidence of hypoglycemia may have been found.

5. The tumors are usually small. They are encapsulated (exception: carcinoma), yellow or red, most often found in the tail.

6. The microscopic appearance is that of adenoma or carcinoma. The cytology of the cells shows insular origin. The beta granules, thought to produce insulin, are present.

7. Other organs show loss of glycogen and fat. The brain shows hyperemia. The changes seen after insulin shock have not been shown.

8. All spontaneous hypoglycemia is not due to pancreatic island tumors. Not all adenomas produce the condition. Resections of the pancreas in the absence of tumor may not stop the attacks. And, finally, they can be produced by disease of other organs.

9. Diabetics with adenomas of the islands may have both hypo and hyperglycemia (dysinsulinism).

10. The typical history is characteristic. A definite sequence of symptoms has been described.

11. The neurological symptoms and findings are the most tangible and the usual initial diagnosis is functional or organic nervous system disease.

12. The blood sugar readings range from .02% to .04% during the attack. In the interval the reading may be normal.

13. The sugar tolerance test is said to be of the diabetic type although this is not constant (?).

14. The B.M.R. in one case was moderately elevated.

15. Diet can control the attacks and intake of food at the onset can abort the seizure.

16. Following operation where adenomas have been found and removed, patients have been relieved. After resections in the absence of adenomas, the patients have not been appreciably benefited.

17. In one case studied, the blood sugar curves became normal after removal of an adenoma.

VI.

Postmortem Blood Chemistry:

Abstr. Rudolph Koucky.

References: Pucher, G. W. and Burd, Lillian A.: A preliminary study of the chemistry of postmortem blood and spinal fluid. Bull. Buffalo Gen. Hosp. 3:11-13, April '25.

The authors ask "---are postmortem blood or spinal fluid analysis of any value in interpreting the premortal chemistry of the patient.?"

It was found that blood from the femoral veins was not clotted even 2o hours after death. It was collected in oxalate. Spinal fluid was taken through an ordinary spinal puncture needle. Bloody samples were discarded. The data obtained by the authors suggests that the chemistry of the postmortem spinal fluid is of value in confirming the premortem blood chemistry. The value of the blood studies is doubtful. The normal concentration of constituents in spinal fluid in relation to blood is as follows:

Urea N	88%
Creatine	46
Uric acid	5
Sugar	75

The postmortem values for uric acid, amino acids and CO_2 fluctuate too greatly both in blood and spinal fluid to be of value. The blood sugar undergoes variable degrees of autolysis but the spinal fluid sugar stays constant. The more constant elements were urea, sugar and creatinine. Urea tends to be high. The authors state that the series is too short and that many factors (such as rapidity of circulation, terminal state, etc.) make the interpretation very difficult. In the series studied, the lowest blood sugar obtained was 40 mgms (20 hours after death). In one case of diabetis with a premortem blood sugar of 140, the postmortem reading was 200. In general, the postmortem blood sugars were very irregular.

NEXT WEEK

APLASTIC ANEMIA