The illness of orthopedic surgeon Dr. Dickinson Ober Wheelock (Figure 1) from Miller, SD, continues to intrigue aficionados of pancreatic islet cell tumors and multiple endocrine neoplasia (MEN) more than 70 years after his death in Rochester, Minn.

Dr. Wheelock underwent surgical exploration by Dr. William J. Mayo in December 1926 for a malignant pancreatic islet cell tumor with hepatic metastases. Extracts of the latter caused hypoglycemia when injected into rabbits, as outlined by Wilder et al. in their classic description of this case in 1927. This case represents the first recorded patient with endogenous hyperinsulinism (insulinoma) to undergo surgical exploration, albeit unsuccessfully.

Recent rereview of the life and premature death of Dr. Wheelock has raised the possibility that he may have had unrecognized MEN 1 (a syndrome not described by Wermer until 1954, 27 years after Wheelock’s death) and that his pancreatic tumor may have been pluripotential, secreting several pancreatic islet cell hormones.

**History**

Dr. Wheelock was initially seen at the Mayo Clinic in 1922, at the age of 41 years; his principal complaint was “trouble with his stomach.” Dr. Charles H. Mayo, consulting physician, believed that mild chronic cholecystitis was present and that no treatment was indicated. Wheelock related that, in 1916 and 1917, while in a field hospital with the American Expeditionary Force in France, he started having “attacks” of severe epigastric pain. These bouts, which lasted several days, were associated with nausea and vomiting, as well as pronounced epigastric tenderness and rigidity. After the more severe episodes, the patient would be “in shock” for several hours, with a slow pulse and great “prostration.”

Because of the severity of these attacks, Dr. Wheelock was evacuated to Fort Snelling in Minneapolis, Minn, where he underwent an operation in February 1918 performed by Dr. Frank C. Mann (of Mann-Williamson ulcer fame). At operation, Dr. Mann encountered severe deformity of the duodenum, with many dense adhesions in this area. A gastroenterostomy was performed for what was thought to be a chronically perforated duodenal ulcer.

Dr. Wheelock returned to Rochester in 1924, complaining of epigastric distress and tenderness, as well as an erythematous puritic rash involving his perineum, penis, and scrotum; he wondered if he had lupus erythematosus. He had had 2 attacks of renal colic and had passed 2 renal stones. Wheelock was seen in consultation with Dr. E. Starr Judd, who concurred with the prior diagnosis of chronic cholecystitis but added, “it seems that a gastroenterostomy was done in a hypersensitive individual without an ulcer ever being documented.” No treatment was advised, and no explanation was given for his perineal rash.

Dr. Wheelock’s next visit to Rochester was in November 1926. He was referred by Dr. D. A. Gregory from Miller and was accompanied by a colleague and friend, Dr. P. McWhorter. Dr. Gregory’s referral letter (Figure 2) is the epitome of descriptive clarity and contains the following remarkable statements:

Dr. Wheelock is a very interesting case and I will give you a very brief and fragmentary history. He was overseas and had a great amount of gastric pain and picked up an Army diagnosis of gastric ulcer and was operated on by Mann at the Army hospital at Minneapolis. Mann stated that he did not find any ulcer but did find numerous adhesions about the gall bladder but did a gastroenterostomy. He was at the Mayo clinic in 1921 and again in 1924 but did not receive any help and was quite dissatisfied. I think someone picked him for a ‘nut’ and he was sent home with advice to take a rest and the usual line of b.s. handed the ‘nuts.’

He had quite a lot of pain in his abdomen and about a year ago he noticed that he would develop a tremor, sweating, and nervousness after going without food or after severe exertion. He discovered that taking sugar would prevent the recurrence of these attacks. At one time, he had some sugar in the urine, but this was probably a renal slop-over and would not occur unless he had a meal very rich in carbohydrates preceding the urine specimen. He was under the care of Ulrich [Dr. George W.] of Minneapolis who stated that he had a hypoglycemia. I have never found sugar in his urine. About three weeks ago, I saw him in one of his typical attacks caused by his going without breakfast and not having enough candy. He resembled an acute alcoholic, great motor activity, dancing and talking, squinting and frowning, apparently...
having hallucination of sight and hearing, negativistic and difficult to control. I had great difficulty in getting him to take a Coca Cola full of syrup, but after taking it, he recovered in about five minutes and the sequel was a very severe cramping in the legs which passed off in about half an hour after taking some sugar. Several times he has become comatose but never has gone far enough so that he could not swallow.

I am very much interested in Wheelock as he is a very fine chap and a very good doctor. He has done quite a bit of surgery but does not have any delusions of grandeur. An interesting thing came to my attention regarding Doctor Wheelock so thought that I would pass it on to you. Dr. E. S. Muir of Winona, who died in 1919, was a cousin of Dr. Wheelock. Dr. Muir’s mother and Dr. Wheelock’s father were brother and sister. Mr. E. D. Wheelock, a brother of Dr. Wheelock, married a lady who was the secretary of Dr. Muir and she definitely states that the attacks of Dr. Wheelock are the same as those that Dr. Muir (a cousin) had (italics added). Dr. Muir’s wife would relieve him and restore him to consciousness by giving him hot, sweet coffee which had also been found efficacious in treatment of Dr. Wheelock. Dr. Muir died in coma following a maniacal attack like those of Dr. Wheelock about four hours after a consultation of his doctors had decided that there was nothing wrong with him except nervousness and had advised rest. [Dr. Muir was seen at Mayo Clinic in 1919, in a severely emaciated state. No diagnosis was made, and no autopsy was performed.]

I know that the tale that I have written you has no value as evidence but Dr. Muir had been a patient at the Clinic and it might be interesting to dig up his history. This man is not a ‘nut’ but has become rather sour ed on his professional confreres because he has not got to first base on a diagnosis. This man Wheelock is an exceptional case and I can find nothing about hypoglycemia. Try and get someone interested in him and don’t let him die because he sure will if he goes too long without carbohydrate.

During Dr Wheelock’s 1926 in-hospital evaluation under the care of noted endocrinologists Drs Russell M. Wilder and Frank N. Allan, the power of history taking and careful documentation is evidenced by the following note by Dr Allan:

One year ago he had a serious attack with complete collapse. This occurred after a hard morning’s work in the operating room. It began with the feeling of weariness then exhaustion. Then he became almost unconscious. He could not respond to questions but has no memory of what happened. He was given an eggnog and quickly recovered. It was then recognized that the attacks were due to hypoglycemia and since then he has taken sugar in some form as soon as the symptoms appeared with immediate relief. The worse attack occurred on March 6 in Minneapolis. He went in for blood sugar tests and had no breakfast. At noon he became unconscious and was resuscitated three hours later by intravenous injection of glucose. His wife watches him very closely and puts candy in his mouth at the first sign of unusual behavior, such as restlessness, peculiar breathing, etc. He gave up work about ten months ago and has spent all of his time looking after himself.

The physicians observing Dr Wheelock realized that large amounts of glucose were needed to maintain an asymptomatic state. In fact, an estimated 25 g of glucose per hour was needed for him to remain symptom free. Because medical treatment could not control the disease
and the patient desired an operation, surgical exploration was performed on Saturday, December 4, 1926, by Dr Will Mayo. The operative dictation reads as follows:

The pancreas was normal from the head to the top of the spine and from then on it curved like a shrimp and seemed to grasp the spine. The consistency of this portion was hard, irregular and had a plastic feel.... The pancreas did not necessarily feel as though there were malignancy but the capsule and all the different parts of the pancreas were involved. Secondarily there is a tumor the size of an orange in the middle of the right lobe of the liver which does not come to the surface.... A specimen about five cm wedge-shaped by about 4 cm at the point of the wedge was removed for diagnosis and given to Dr. Powers [Figure 3]. The gall-bladder was greatly distended and buried in a mat of adhesions. It was the size of a Bartlett pear, did not empty readily and contained a number of papillomata. The gastroenterostomy was alright but there was marked spasm of the pylorus.

The Inquiring Mind

Struck by the similarity of the patient’s hypoglycemic attacks with the spells of insulin shock, Dr Wilder and colleagues prepared extracts of both the tumor and the normal liver and injected these into the ear vein of 2 rabbits. The results are intriguing (Table 1).

Based on this experiment, the carcinomatous tissue yielded at least 40 U of insulin per 100 g of tissue. These early inquiring minds ruminated:

![Figure 2. Dr D. A. Gregory’s original referral letter, October 28, 1926.](image)

[T]he extract from the tumor behaved exactly like an insulin preparation on injection into rabbits. A more plausible possibility is that small amounts of insulin were being liberated continuously whether the blood sugar was high or low, that is, irrespective of the need for insulin.

Biochemistry

Preoperatively, biochemical investigations concentrated on the patient’s serum glucose level and its relationship to administration and deprivation of glucose. Unfortunately, a serum calcium level was not obtained, although hypophosphatemia, with serum phosphate levels of 2.1 to 2.6 mg, was documented.

Postoperative Course

Dr Wheelock did poorly after surgical exploration. He required constant oral candy and glucose infusion. He died (without leaving the hospital) on January 3, 1927, “of no apparent reason than exhaustion. He was conscious and entirely rational to within a few minutes of death.”

An autopsy (performed 3 hours after death) confirmed the presence of a carcinoma of the pancreas with metastases to the liver, intestine, and regional lymph nodes. The prosector described the pancreas on cut section as “seen to contain yellowish irregular nodules varying from a few mm to 1.3 cm, which are surrounded by a dense greyish connective tissue.”
Figure 3. Photomicrographs of low (A) and intermediate (B) magnification, showing metastatic deposits of islet cell tumor. Tumor is composed of cuboidal epithelial cells arranged in a distinctive “neuroendocrine” pattern that includes ribbons and nests (hematoxylin-eosin).

No mention was made about the presence of either normal or abnormal parathyroid glands, although this is not surprising because the first operation on parathyroid glands at the Mayo Clinic would not occur for 7 more years.

Discussion

Dr Wheelock definitely had an insulin-secreting islet cell carcinoma of the pancreas, which was responsible for his classic spells and, perhaps, for some of his epigastric distress of more than 10 years' duration. However, did the carcinoma also secrete other hormones? Is there credible evidence to suggest that he might have had MEN 1? The following evidence in connection with the known effects of functioning pancreatic islet cell tumors and their familial occurrence is pertinent.

1. Severe attacks of epigastric pain in a 36-year-old man led to abdominal exploration, with evidence to suggest prior duodenal ulcer perforation—? Zollinger-Ellison syndrome-hypergastrinemia.

2. Nephrolithiasis and pronounced hypophosphatemia were present—? primary hyperparathyroidism-parathyroid hormone secretion.

3. Unequivocal endogenous insulin production was noted—insulinoma.

4. An erythematous, pruritic perigenital/genital rash was evident—? necrotizing migratory erythema-glucagon secretion.

5. A cousin (Dr Muir) had attacks identical to those experienced by Dr Wheelock—? familial connection.

We were excited and hopeful that the archival formalinized tissue might enable us to perform DNA analysis and search for the presence of the MEN\] gene (menin). Unfortunately, the tissue was so denatured that this was not feasible. Equally frustrating is the fact that we have been unable to find any other members of the Wheelock family who may have died of MEN 1-related causes. Despite an exhaustive search, few members of the Wheelock family were found, and thus our data are incomplete.

We suggest, however, that the evidence we have adduced supports the theory that Dr Wheelock may have been a member of a family with MEN and that he unfortunately died at a young age because of the complications of this complex and rare syndrome.

Acknowledgment

We want to acknowledge the valuable advice that we received in the preparation of this article from Drs Jeffrey L. Myers and J. Aidan Carney, pathologists extraordinaire.

Table 1. Effects of Tissue Extracts on the Blood Sugar of Rabbits*

<table>
<thead>
<tr>
<th>Material injected</th>
<th>Blood sugar (mg/dL)</th>
<th>0 h</th>
<th>1.5 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (2 U)</td>
<td>127</td>
<td>72</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Liver extract</td>
<td>121</td>
<td>125</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Tumor extract</td>
<td>118</td>
<td>47</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

*Data from Wilder and associates.\(^1\)

REFERENCES
