A survey of the literature reveals that cases of primary carcinoma of the liver are not uncommon, although the clinical diagnosis is difficult. It is infrequently made except by an exploratory operation or at post-mortem examination. The incidence of this lesion associated with hypoglycemia is, on the other hand, exceedingly rare. Boyce and McFetridge (1) in a recent review report 28 cases of carcinoma of the liver, making the total available in print at the present time well over six hundred. Yet among this number are only two cases of primary liver-cell carcinoma associated with hypoglycemia. One of these is reported by Crawford (2), the other by Elliott (3) and by Nadler and Wolfer (4). It is our purpose to review the literature on this subject briefly and to add to it a single case of this syndrome.

The case reported by Nadler and Wolfer (4) was that of a thirty-year-old colored male with the diagnosis of primary carcinoma of the liver proved by exploratory operation. Attacks similar to insulin shock were frequent, and were associated with an average blood sugar of less than 50 mg. per cent. Hourly feedings of 18 gm. glucose in addition to a basic diet furnishing 440 gm. of carbohydrate were necessary to keep the patient alive. The man lived slightly over three months. At autopsy a tumor replacing more than 70 per cent of the liver substance was found. Metastases were present in the lungs and in the mediastinal nodes. The pancreas showed no pathologic changes and on analysis contained a low percentage of insulin. Neither insulin nor glycogen was extracted from the tumor, and the liver tissue contained only 0.8 per cent glycogen. The tumor cell was reported as polyhedral, smaller and darker than the liver cell. The cells were arranged in cords and masses about vascular sinuses and were supported by a fine fibrous stroma.

Crawford's (2) case also occurred in a colored male, aged forty-three, who gave a history of abdominal trauma six weeks prior to observation. Episodes similar to insulin shock were frequent and were relieved only by administration of 1700–2200 gm. glucose daily. The blood sugar was uniformly below 50 mg. per cent, but no other evidence of liver damage was determined. This man lived sixteen days. At autopsy a medullary carcinoma of the liver, replacing about 70 per cent of the organ, was found. The entire mass weighed 4150 gm. Metastases were present in the lungs. The tumor architecture was described as large alveoli of medium-sized, undifferentiated cells obliterating the liver structure. The pancreas appeared normal. No analysis of any tissue for insulin or glycogen was done.
To the above we wish to add the following report.

Case Report

J. W. (No. SSSSS), a sixty-five-year-old white male tobacconist, was admitted to the Strong Memorial Hospital on May 9, 1934. For several days prior to admission the man had observed that on awaking he felt weak, dizzy, and faint and that there was a peculiar numbness in his hands and feet. These symptoms were invariably relieved by food, but recurred in a few hours. On the morning of entry, the symptoms were more pronounced than usual, but the patient managed to get dressed and out into the street in search for food before falling unconscious.

When seen in the hospital he was in coma, breathing irregularly; the pulse was regular and rapid; the blood pressure was 160 systolic and 80 diastolic. He was sweating profusely, and the skin showed a peculiar bronzed pallor. The heart and lungs were essentially normal but a large, hard, nodular mass extending down to the umbilicus filled the right upper quadrant. Inconstant pyramidal tract signs were present. The blood sugar at this time was 31 mg. per cent, but immediately following the intravenous administration of 50 gm. of glucose the patient became alert and rational.

Laboratory studies showed blood sugar values ranging from 10 to 50 mg. per cent; hemoglobin 16.4 gms.; red blood cells 4,900,000; white blood cells 13,000, with 92 per cent polymorphonuclear cells. The urine was repeatedly sugar-free, although traces of acetone and albumin were frequently observed. Non-protein nitrogen of the blood was 10 to 25 mg.; carbon dioxide combining power measured 50-65 vols. per cent. The blood calcium was 9.8, and phosphorus 3.9; the icteric index was 14, serum albumin 3.7, globulin 2.4, fibrinogen 396. A sugar-tolerance test showed a blood sugar of 35 mg. per cent two hours after 100 gm. of glucose had been taken by mouth. A bromsulphthalein test showed 50 per cent of the dye retained in five minutes and 20 per cent in thirty minutes. A phenosulphonephthalein test showed 72 per cent dye excretion in two hours. Wassermann and Kahn tests were negative. Stools were negative.

In the hospital there was a progressive tendency for hypoglycemic syncope to occur. It was necessary to give drinks containing 40 gm. of glucose every hour in addition to a diet furnishing 250 gm. of available carbohydrate. Occasional intravenous injections of glucose were needed to bring the patient back from acute collapse. A diagnosis of hyperinsulinism from a tumor of the islets was considered, although the large nodular liver could not be overlooked as evidence of possible malignancy of that organ. An exploratory laparotomy was performed under local anesthesia on May 24, 1934. At that time the pan-
FIG. 2. NODULE OF TUMOR SHOWING CORDS OF LARGE POLYHEDRAL CELLS SURROUNDING BLOOD SINUSES
In the center may be seen strands of liver cells in a fibrous stroma. x 38.

FIG. 3. HIGH-POWER MAGNIFICATION OF SECTION SHOWN IN FIG. 2, SHOWING LARGE UNDIFFERENTIATED TUMOR CELLS, MANY VACUOLATED CELLS, AND THE RELATION OF THE TUMOR TO BLOOD SINUSES. x 280
creas appeared normal, but the liver was largely replaced by nodules of tumor tissue. Biopsy revealed a primary liver-cell carcinoma. The course was unchanged for the first two postoperative weeks, but the relapses became more and more frequent and were associated with chills and fever as high as 41° C. In the course of the next month the patient became weaker and weaker, finally contracting bronchopneumonia. He died on June 29, 1934, seven weeks after admission. The liver by this time had extended to the pelvis and nearly filled the upper abdomen. The terminal blood sugar was 18 mg. per cent.

Autopsy was performed by Dr. H. B. Slavin. The heart showed a healed mitral endocarditis. The lungs showed patchy congestion and bronchopneumonia. The lower lung fields were studded with small gray nodules 1 to 2 mm. in diameter with caseous centers which subsequently proved to be tubercles. The liver weighed 4500 gms. The peritoneal and cut surfaces (Fig. 1) were studded with green gray nodules 0.5 to 5 cm. in diameter. About 75 per cent of the liver substance was replaced by the tumor tissue, but small areas of cirrotic distorted liver tissue were discernible between the tumor nodules. The pancreas, adrenals, spleen, and other organs showed no pathologic change either grossly or microscopically.

Sections taken from the nodes at the hilus of the lungs and that of the liver showed adenocarcinomatous infiltration. Sections from the liver nodules (Figs. 2 and 3) showed a pleomorphic cell type, the commonest being a large polyhedral cell with large vesicular nucleus and pale staining granular cytoplasm which was vacuolated (fat). Mitotic and amitotic division was frequent, and an occasional giant cell was seen. Faint acini, cords and strands of cells surrounded vascular sinuses and were supported by a fine fibrous stroma. The liver tissue showed increased fibrous elements containing round and wandering cells supporting irregular cords of hypertrophic liver cells. Small encapsulated areas of regenerating liver tissue and expanses of hyaline tissue were also present. Tumor tissue was analyzed for insulin, but none was found. The pancreas contained 110 units/kilo, a low normal reading. Unfortunately neither liver nor tumor was analyzed for glycogen content. Thus both clinically and pathologically there was evidence of considerable liver damage which presumably explained the clinical picture. This picture coincides with that described by Ewing as a multiple liver-cell carcinoma.

This tumor is usually associated with some degree of cirrhosis and may occur in either single or multiple form. Some resemblance of the tumor to liver cells is usually discernible. As described, the growth is of high malignancy, although distant metastases are not common, the lung and regional nodes being most frequently involved. In our case, with the exception of the loss of architecture, the similarity to a fatty liver was remarkable.

Discussion

Many reports of hyperinsulinism have been made since the confirmation of Harris’ (5) theory by Wilder and associates (6) in the description of a case of carcinoma of the islands. Two classes of causative factors producing low blood sugar with its symptoms may be cited: (1) excess production of insulin; (2) derangement of the glycogen storage mechanism. In the first group may be placed carcinoma of the islets, as noted by Wilder (6), Thalhimer and Murphy (7), and others; benign adenoma as recorded by McClenahan and Norris (8); or simple hypertrophy as recorded by Finney and Finney (9). In the second group, mechanical or chemical impairment of glycogen storage function of the liver has been observed. Cross and Blackford (10) reported this syndrome following arsenic poisoning. Toxic states, acute yellow atrophy, and fatty metamorphoses have been mentioned by Howard (11), Judd (12), and Ryman (13) as causing symptoms similar to insulin shock. Vascular changes, such as thrombosis of the hepatic
artery, have also been described by Pollack and Long (14). According to Rynearson (15) cases of this second group have been erroneously designated hyperinsulinism. We would place our case and those of Crawford and Wolfer in this group, as there was definite clinical and pathological evidence of liver damage. It is hard to believe that 1000 gm. of glucose should be necessary to maintain daily metabolism and at the same time have the blood sugar so uniformly low, despite the fact that there was no overproduction of insulin either by the pancreas or by the tumor. The answer must lie in some as yet undiscovered phase of carbohydrate metabolism.

**Summary**

A case of primary liver-cell carcinoma is presented which is distinguished by hypoglycemia due to impaired liver function. A brief review of the only two similar reported cases is given. A short discussion of the various causes of hypoglycemia due to organic abdominal pathology is included.

**Bibliography**