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HEPATIC HYPOGLYCEMIA*

Its Occurrence in Congestive Heart Failure

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MANN'S[1] classic experiments in 1921 first demonstrated that a normal concentration of blood sugar in the hepatectomized animal can be maintained only by a constant infusion of glucose. Spontaneous hypoglycemia has been described in man in cases of obvious liver damage due to cirrhosis, viral hepatitis, chemical poisoning, carcinoma and other processes.[2] Nevertheless, experience with various forms of liver disease at the Johns Hopkins Hospital indicates that episodes of hypoglycemia are frequently overlooked. Furthermore, it is not well appreciated that hepatic hypoglycemia may occur in the absence of other apparent evidence of impaired liver function. Conn et al.[3] first made this important observation in 6 patients with cholangitis. Hepatic hypoglycemia is often overlooked as an explanation for mental peculiarities, convulsions or coma. The fact that such oversight precludes the simple and effective treatment employed so long ago by Mann, is emphasized by experience with 20 patients with hepatic hypoglycemia recently seen at the Johns Hopkins Hospital. These 20 cases are briefly presented to emphasize the fact that hepatic hypoglycemia is not uncommon and may appear in a variety of circumstances, sometimes without other overt indications of extensive liver disease.

Case Reports

Case 1. D. B. (J.H.H. 265370), a 27-year-old Negress, became anorexic and jaundiced 4 months after receiving several blood transfusions in the treatment of an abdominal stab wound. Physical examination was not remarkable except for jaundice. The laboratory studies were noteworthy only in the findings consistent with the diagnosis of homologous serum jaundice: +++ cephalin-flocculation test; thymol turbidity of 23 units; alkaline phosphatase of 7.2 Bodansky units; and a serum bilirubin of 11.8 mg. per 100 cc. Three days after admission to the hospital, the patient became drowsy, incontinent of urine and combative, and did not recognize her friends. Some observers thought schizophrenia had developed. When the blood sugar was found to be 44 mg. per 100 cc., glucose was given parenterally. Immediately, the patient became rational, remaining so throughout an uneventful recovery from the hepatitis. Subsequent blood sugar determinations were always above 70 mg. per 100 cc.

Except for the episode of disordered behavior, this patient was no more severely ill than many others with hepatitis, nor were the usual chemical indications of liver disease remarkable.

Case 2. J. P. (J.H.H. 181318), a 65-year-old Negress, experienced chills and fever after dilatation of a ureteral stricture and was admitted to the gynecologic service. For many years she had been treated for chronic pyelonephritis and mild diabetes mellitus. She was known to be a chronic alcoholic; and while receiving her customary 10 units of protamine zinc insulin daily she had several insulin reactions on the ward. The drug was therefore discontinued. Fever disappeared with the administration of Gantrisin and intravenous injection of fluids. Forty-eight hours after all insulin had been discontinued, the fasting blood sugar was 138 mg. per 100 cc., and the patient was quite rational. At 8 p.m., having received approximately 85 gm. of sugar intravenously during the day, she lapsed into profound coma; she lay motionless and was drenched with perspiration. The only other striking physical finding was a hard liver edge 2 fingerbreadths below the right costal margin. Blood was drawn for sugar determination, and 40 cc. of 50 per cent glucose was rapidly injected. The patient immediately awakened, and the blood sugar was subsequently reported to be 8 mg. per 100 cc. Blood chemical studies were as follows: serum bilirubin, less than 0.8 mg. per 100 cc.; alkaline phosphatase, 6.4 Bodansky units; cephalin flocculation, ++; thymol turbidity, greater than 31 units; prothrombin time, 40 per cent of normal; and nonprotein nitrogen, 90 mg. per 100 cc. Careful attention was paid to the intravenous administration of glucose; the patient never again became hypoglycemic, but she eventually died in uremia. Autopsy disclosed chronic pyelonephritis, Kimmelstiel–Wilson lesions in the kidneys, generalized and coronary arteriosclerosis, encephalomalacia and moderately advanced Laënnec's cirrhosis of the liver. The pancreas contained an occasional hyalinized islet and numerous areas of atrophy and focal scarring secondary to squamous metaplasia of the pancreatic ducts, but no islet cell-adenoma or hyperplasia.

It is true that this patient had received insulin prior to the hypoglycemic coma, but forty-eight hours had elapsed since the last injection of insulin, when only 10 units were given, and the morning before she lapsed into coma the fasting blood sugar was 138 mg. per 100 cc. Autopsy gave no explanation for the hypoglycemia other than the liver disease, and although the cirrhosis was moderately severe and involved the entire organ, it had not previously

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caused any clinical difficulty, nor was the patient jaundiced at any time.

Case 3. B. E. (J.H.H. 535946), a 38-year-old woman, had an 18-month history of a peculiar form of heart failure manifested chiefly by dyspnea and spells of weakness and syncope. She presented signs of congestive heart failure and mental confusion. The day after admission she lapsed into coma. The blood sugar at that time was 23 mg. per 100 cc., and after the administration of 50 cc. of 50 per cent glucose intravenously she roused transiently, but subsequently died in shock. The following liver-function tests were reported: bromsulfalein retention, 16 per cent in 55 minutes; serum bilirubin, 0.5 mg. per 100 cc.; thymol turbidity, 4.5 units; serum albumin, 3.6 gm. per 100 cc.; and serum globulin, 3.4 gm. per 100 cc. The striking finding at autopsy was a myxoma of the left auricle. There was also passive congestion of the viscera, including the liver, and the type of central hepatic necrosis often found in patients dying of heart failure.

Cerebral anoxemia of varying degree is a frequent occurrence in congestive heart failure, and is commonly believed to account for any alterations of consciousness. This case demonstrates that hepatic hypoglycemia may be associated with congestion of the liver in heart failure, in the absence of jaundice. One wonders how many patients with "cardiac coma" may be suffering from hypoglycemia while the attention of the physician is focused not upon the liver but upon the heart.

Case 4. F. H. (J.H.H. 369902), a 70-year-old Negro, was found at operation to have adenocarcinoma of the head of the pancreas, with metastases to the liver and biliary cirrhosis. A cholecystogastrostomy was performed, and the serum bilirubin fell from 17 to 5 mg. per 100 cc. The patient convalesced at home, feeling weak but rational and communicative. One morning he was found by his family in deep coma. An hour later he was brought to the hospital and given 25 gm. of sugar intravenously. He sat up and spoke rationally. A blood sugar determination before the administration of glucose was 6 mg. per 100 cc. The patient ate a fair meal, was able to walk without assistance and, at his request, returned to his home.

Unfortunately, this patient's subsequent course is unknown to us, but the hypoglycemic episode observed re-emphasized the extent to which the blood sugar may fall in a patient whose liver disease is not otherwise incapacitating.

Case 5. J. L. (J.H.H. 176606), a 71-year-old Negro, had been treated in the Johns Hopkins Hospital on many occasions for congestive heart failure. He also had a peripheral blood picture suggestive of chronic myelogenous leukemia, treated syphilis and a history of alcoholism. He was uncooperative, and his visits to the clinic were sporadic. One morning, having been ambulatory during the previous day, he was found comatose by friends. The blood pressure was unobtainable, and he was completely unresponsive. In addition, he had anasarca, rales at the lung bases and an enlarged liver. Despite the administration of plasma and glucose he soon died. Blood chemical findings before treatment were as follows: nonprotein nitrogen, 44 mg. per 100 cc., blood sugar, 20 mg. per 100 cc.; carbon dioxide combining power, 18.3 milliequiv. per liter; serum chloride, 84 milliequiv. per liter; and serum bilirubin, 2.9 mg. per 100 cc. Autopsy disclosed syphilitic aortitis, myocardial scars, cardiac dilatation, lobular pneumonia, pulmonary edema and myeloid hyperplasia of the bone marrow. The liver showed marked passive congestion, fatty infiltration in the central portions of the lobules and fine scarring suggestive of early cirrhosis.

The cause of this patient's myocardial disease is not clear from the autopsy findings. It is obvious, however, that he had liver damage that was due at least in part to chronic heart failure, and possibly also due to alcoholism. The liver disease, which was the only apparent reason for the hypoglycemia, had never clinically been a major problem in the patient's long illness.

Case 6. A. R. (J.H.H. 546233), a 37-year-old woman, had for 10 years consumed about ½ pint of whiskey daily. She was admitted to the hospital with hepatomegaly, edema of the legs and ascites. She was confused and disoriented and had paranoid delusions about other patients and the attending physicians and nurses. She was thought to have Laënnec's cirrhosis and a "toxic psychosis due to alcoholism." Blood chemical values were as follows: serum bilirubin, 6 mg. per 100 cc.; cephalin flocculation, ++++; thymol turbidity, 3.2 units; alkaline phosphatase, 17.5 Bodansky units; prothrombin time, more than 80 per cent of normal; serum cholesterol, 254 mg. per 100 cc.; fasting blood sugar, 48 mg. per 100 cc. Because of delay in receipt of the last report, hypoglycemia was not recognized, but the patient was encouraged to eat frequently, having consumed little but alcohol prior to admission. Within 48 hours she was rational and has remained so during the 18 months of follow-up observation. All subsequent blood sugar determinations have been normal. Ascites and edema disappeared within 1 month, and the liver-function tests gradually improved. Three weeks after admission the cephalin flocculation was 0, thymol turbidity 2.5 units, alkaline phosphatase 7.2 Bodansky units and bilirubin 1.8 mg. per 100 cc. The liver edge is no longer palpable, and liver-function tests are all within normal limits.

Again, there is no pathological proof, but there is compelling clinical evidence, that this patient had reversible alcoholic and dietary liver damage. The hypoglycemia may have been partially the consequence of poor eating, but was almost certainly a manifestation of liver disease. This case illustrates how the mental reaction resulting from hypoglycemia may be confused with some other psychosis. The opportunity for prompt and efficient therapy with intravenous administration of glucose was missed; it was fortunate that the dietary treatment of alcoholic cirrhosis is also a means of correcting hepatic hypoglycemia.

Case 7. L. T. (J.H.H. 532035), a 40-year-old woman who was a chronic alcoholic, was proved by biopsy to have cirrhosis of the liver. On 8 occasions during 9 weeks' hospitalization for recurrent jaundice, the fasting blood sugar ranged between 56 and 64 mg. per 100 cc. At no time, however, were there recognizable symptoms of hypoglycemia. The results of liver-function tests were as follows (the paired figures representing the values at the beginning and at the end of hospitalization respectively): serum bilirubin, 14.5 to less than 0.8 mg. per 100 cc.; serum alkaline phosphatase, 13.4 to 8.6 Bodansky units; cephalin flocculation, +++ to ++; thymol turbidity, 29.2 to 22 units; serum albumin, 2.9 to 3.1 gm. per 100 cc.; serum globulin, 4.0 to 3.5 gm. per 100 cc.; and prothrombin time, 30 to 35 per cent of normal. In the 2d month of hospitalization, a glucose tolerance test was performed, with the following results: fasting, 64, ½ hour, 180, 1 hour, 170, 1½ hours, 48, 2 hours, 24, 3 hours, 52, 4 hours, 64, and 5 hours, 68 mg. per 100 cc. During the period when the blood sugar values were 48, 24 and 52 mg. per 100 cc., the patient exhibited marked sweating, confusion and obtundity, but she recovered spontaneously and appeared mentally normal during the 4th and 5th hours of the test.

In this case there were no symptoms or signs of hypoglycemia, apart from those observed during the glucose tolerance test, despite the repeated finding of a slightly low fasting blood sugar. During the glucose tolerance test, however, marked lowering of the blood sugar was accompanied by sweating and obvious cerebral dysfunction.

A period of hypoglycemia following the initial elevation of the blood sugar during a glucose tolerance curve is observed in patients with hepatic disease, and those with so-called functional or reactive hypoglycemia. It seems unlikely that in this patient with diffuse liver disease reactive hypoglycemia was the major cause of the low blood sugar values. Seldom, if ever, is simple reactive hypoglycemia associated with persistent fasting hypoglycemia, nor is the blood sugar often as low as 24 mg. per 100 cc. In all likelihood the delayed hypoglycemia was due to the liver disease. The findings in this case indicate the need for a careful study of liver function in patients suspected of having "functional" hypoglycemia.

Case 8. J. H. B. (J.H.H. 413182), a 58-year-old Negro, underwent a total pancreatectomy and cholecystojejunostomy because of an adenocarcinoma of the pancreas. For 2 months postoperatively the "surgical diabetes" was treated with moderate doses of crystalline and protamine zinc insulin. Because of numerous hypoglycemic episodes considered to be insulin reactions, the insulin was discontinued. He ate poorly and was fed principally by infusions of sugar. A week later the urine was acetone free, and the fasting blood sugar was 156 mg. per 100 cc. On the following day the fasting blood sugar was 25 mg. per 100 cc. and he was promptly roused from coma by the intravenous administration of glucose, of which, during the day, he received a total of 5000 cc. of a 10 per cent solution. In the ensuing 2 days, having received no insulin, he was given 800 cc. of 50 per cent glucose and 1500 cc. of 5 per cent glucose intravenously. Nevertheless, when the infusion was discontinued for 1 night, he lapsed into a coma, from which he never recovered. The blood sugar after the night's "fast" was 12 mg. per 100 cc. Blood chemical values in the final week of illness were as follows: serum bilirubin, 38 mg. per 100 cc.; cephalin flocculation, +++; thymol turbidity, 8.5 units; serum cholesterol, 252 mg. per 100 cc.; serum alkaline phosphatase, 55.6 Bodansky units; prothrombin time, 45 per cent of normal; and serum albumin 3.2 and serum globulin 2.6 gm. per 100 cc. Autopsy disclosed metastatic adenocarcinoma of the pancreas in the liver and lungs, biliary cirrhosis and central atrophy of the liver, chronic cholecystitis and a torn hepatic duct (apparently a surgical accident).

This unfortunate patient had severe, resistant hypoglycemia secondary to widespread liver disease. Insulin had been discontinued nine days before his death, and could not have been responsible for the final blood sugar level of 12 mg. per 100 cc. On the contrary, it seems far more likely that the numerous "insulin reactions" early in the course were at least partially caused by the liver damage. In this case hepatic hypoglycemia appeared despite total pancreatectomy. Similarly, in pancreatectomized dogs, which are ordinarily diabetic, hepatectomy produces fatal hypoglycemia.[1]

Case 9. W. R. (J.H.H. 280018), a 30-year-old Negro, had been followed at this hospital for many years because of sickle-cell anemia. His last admission followed a 36-hour period of dyspnea and intense back pain. Congestive heart failure was manifested by pulmonary and peripheral edema, and the liver edge was palpable 6 cm. below the right costal margin and 13 cm. below the sternum. The hematocrit was 19 per cent; the white-cell count was 38,000 with 8 per cent reticulocytes, and there was approximately 36 per cent immediate sickling of the red cells. The serum bilirubin was 20 mg. per 100 cc., cephalin flocculation +++, thymol turbidity 14.3 units, and alkaline phosphatase 6.6 Bodansky units. Shortly after admission the patient lapsed into coma, had generalized convulsions and died. A blood sugar determination on a sample drawn during the coma, but not reported until after death, was 23 mg. per 100 cc. Autopsy demonstrated atrophy and fibrosis of the spleen, "sickle-cell nephritis," recanalized pulmonary thrombi, cor pulmonale, pulmonary and cerebral edema, nodular cirrhosis of the liver, with hemosiderosis, hemosiderosis of the pancreas and kidney, aspiration pneumonia and an acute gastric ulcer.

This case has many points of interest not germane to the present discussion, but illustrates once again that severe hepatic hypoglycemia may appear when other clinical abnormalities are more prominent and obvious.

Case 10. J. C. E. (J.H.H. 595114), a 19-year-old boy, a chronic alcoholic, was admitted to the hospital with a 3 weeks' history of jaundice, malaise and anorexia. Two of his brothers had died of hepatic necrosis, and another brother appeared to be recovering from severe infectious hepatitis. The patient was obviously very sick, with nausea, vomiting, jaundice, low-grade fever and a liver edge palpated 4 fingerbreadths below the right costal margin. The serum bilirubin on admission was 11.2 mg. per 100 cc. and shortly before death 1 week later, 29 mg. per 100 cc. The cephalin flocculation was +++, thymol turbidity 8.2 units, alkaline phosphatase 5.6 Bodansky units, serum albumin 2.9 and serum globulin 3.0 gm. per 100 cc., prothrombin time less than 20 per cent of normal, nonprotein nitrogen 44 mg. per 100 cc., and fasting blood sugar 68 mg. per 100 cc. Despite intravenous injection of glucose and serum albumin, the patient gradually became weaker and more jaundiced. On the day of death he lapsed into coma. A blood sugar determination was 23 mg. per 100 cc. The patient rallied and became lucid after the intravenous administration of glucose, but then, despite continued glucose infusions, again sank into coma and died several hours later. Autopsy showed severe chronic hepatitis.

In this case hypoglycemia was associated with liver failure so severe that intravenous administration of glucose was of only transient value. The situation is reminiscent of Mann's hepatectomized dogs, in which consciousness preserved with intravenous administration of glucose was followed in a day or so by irreversible coma.[1]

Case 11. M. C. (J.H.H. 594910), a 70-year-old woman, was admitted to the hospital in severe congestive heart failure. Four years before admission mild exertional dyspnea, which gradually became worse, had developed, and for 1 year before admission she had been treated with digitalis and mercurial diuretics because of increasingly severe exertional dyspnea, orthopnea and ankle edema. Despite these therapeutic measures the congestive heart failure became much more severe in the month before admission, and in the 5 days preceding admission mild confusion had slowly turned into stupor and nearly complete loss of reason. The important findings on physical examination were cyanosis of the fingers, toes and lips, distended neck veins, marked edema of the ankles and back, rales at both lung bases, enlargement of the heart, with harsh systolic murmurs suggestive of mitral and aortic disease, a tender liver edge palpated 3 fingerbreadths below the right costal margin and very little responsiveness to any stimuli. The patient did not improve in an oxygen tent or in a sitting position in a "cardiac bed." The hematocrit was 56 per cent and the white-cell count 12,000. The urine was remarkable only for a ++ test for albumin and urobilinogen found in 1:200 dilution. The patient's mental status was ascribed to cerebral anoxia, but because of her age and critical condition various blood chemical values were determined. These were as follows: nonprotein nitrogen, 98 mg. per 100 cc.; blood sugar, 16 mg. per 100 cc.; carbon dioxide combining power, 21.6 milliequiv. per liter; and serum chloride, 100.2 milliequiv. per liter. Almost immediately after 50 cc. of 50 per cent glucose had been rapidly injected intravenously, the patient became much less lethargic and disoriented. Thereafter, the blood sugar was maintained above 100 mg. per 100 cc. by slow infusions of 10 per cent glucose and oral feeding, but despite all measures to improve her cardiac and renal status, the nonprotein nitrogen rose to 134 mg. per 100 cc., and the heart failure became progressively more severe. Marked mental clouding returned on the 3d hospital day; the patient lapsed into coma and died on the 4th hospital day. Before death the following determinations were made: serum bilirubin, 3 mg. per 100 cc.; serum albumin, 3.1, and serum globulin, 2.3 gm. per 100 cc.; cephalin flocculation, +++; and thymol turbidity, 5.3 units. At autopsy the principal findings were calcific aortic stenosis and mitral stenosis, generalized arteriosclerosis and passive congestion of all the viscera, including the liver, which showed marked central necrosis. There were a few small areas of infarction in the pituitary gland, but these were not considered significant by the pathologist, who pointed out that such lesions are not uncommonly found at autopsy in patients having no clinical evidence of pituitary dysfunction and that the vast majority of the pituitary tissue in this case appeared quite normal.

There can be little doubt that this patient had severe hepatogenic hypoglycemia. It is of interest that the coma, promptly but temporarily relieved by intravenous injection of glucose, was thought to be a consequence of cerebral anoxia until a "routine" blood sugar determination was reported.

The remaining 9 of the 20 cases of hepatic hypoglycemia (summarized in Tables 1 and 2) are not presented in detail because of their similarity to those described above.

Discussion

Transient hypoglycemia was an important feature in the illness of the patients described above (Table 1). In some cases the episodes of hypoglycemia critically affected the course, contributing to death. It seems reasonable to conclude that impaired liver function was the common cause of these periods of hypoglycemia, since other factors capable of inducing hypoglycemia were absent, and all patients had significant liver disease.

Spontaneous hypoglycemia may occur in the following conditions: islet-cell tumor of the pancreas; hyperplasia of the islands of Langerhans, without adenoma formation; reactive or functional hypoglycemia; adrenal insufficiency; pituitary insufficiency; hypothyroidism; extreme muscular exertion, such as marathon racing; liver disease; and during periods of starvation.[4, 5] Of the 20 cases reported in this paper, autopsies were performed in 13, and in none was there evidence of hyperplasia or adenoma of the islands of Langerhans, adrenal

Table 1. *Summary of Cases of Hepatic Hypoglycemia.*

Case No.	Patient	Age	Sex	Liver Disease	Other Diagnoses	Fasting Blood Sugar	Symptoms of Hypoglycemia
		yr.				*mg./100 cc.*	
1	D. B.	27	F	Serum hepatitis	None	44	Schizophrenia-like psychosis
2	J. P.	65	F	Laënnec's cirrhosis	Alcoholism, chronic pyelonephritis, generalized arteriosclerosis and Kimmelstiel-Wilson's disease	8	Coma
3	B. E.	38	F	Passive congestion	Myxoma of left auricle	23	Coma
4	F. H.	70	M	Biliary cirrhosis; metastatic carcinoma.	Adenocarcinoma of pancreas	6	Coma
5	J. L.	71	M	Passive congestion, fatty infiltration and early cirrhosis	Alcoholism, syphilitic aortitis, myocarditis and myeloid hyperplasia	20	Coma
6	A. R.	37	F	Laënnec's cirrhosis	Alcoholism, syphilitic aortic regurgitation and polyneuritis	48	Schizophrenia-like psychosis
7	L. T.	40	F	Laënnec's cirrhosis	Alcoholism	24	Confusion
8	J. H. B.	58	M	Biliary cirrhosis; metastatic carcinoma.	Adenocarcinoma of pancreas (total pancreatectomy)	12	Coma
9	W. R.	30	M	Cirrhosis	Sickle-cell anemia	23	Coma; convulsions.
10	J. C. E.	19	M	Infectious hepatitis	Alcoholism	23	Coma (cholemic coma supervened)
11	M. C.	70	F	Passive congestion	Mitral and aortic stenosis	16	Coma
12	J. H.	21	M	Passive congestion	Constrictive pericarditis; lobar pneumonia.	22	Torpor
13	I. B.	41	M	Laënnec's cirrhosis	Alcoholism, syphilitic aortic regurgitation and polyneuritis	31	Coma
14	G. G.	45	M	Primary hepatoma	Alcoholism; acute bacterial endocarditis.	44	Disorientation (cholemic coma supervened)
15	M. G.	52	F	Infectious hepatitis	None	56	Faintness and palpitation
16	L. R.	41	M	Infectious hepatitis	None	47	None
17	L. S.	25	F	Fatty infiltration	Infection and gangrene of vulva; tuberculous peritonitis; and enteritis.	20	Coma
18	J. S.	45	F	Hepatitis	None	44	Irrational behavior
19	P. H.	32	M	Fatty infiltration	Partial pancreatectomy; subphrenic abscess.	40	Weakness and faintness
20	H. K.	37	F	Passive congestion	Mitral stenosis; ball-valve thrombus of left auricle.	19	Coma

Table 2. *Types of Liver Disease Associated with Hypoglycemia.*

Disease	No. of Patients
Viral hepatitis	5
Laënnec's cirrhosis	5
Chronic passive congestion, with heart failure	5
Biliary cirrhosis	2
Fatty infiltration	2
Primary hepatoma	1
Total	20

damage, thyroid disease or pituitary abnormality, except in Case 11, whose insignificant pituitary damage is explained in detail above. All, however, showed unequivocal diffuse hepatic damage on histologic examination. Moreover, there was clinical or laboratory evidence of liver disease apart from the hypoglycemia in all 20 patients, although in some cases liver impairment had not been considered a significant feature of the illness. On the other hand, in none of these patients were there clinical indications of pituitary, adrenal or thyroid insufficiency, nor could extreme exercise, prolonged starvation or reactive hypoglycemia have played an important part in the development of these hypoglycemic states. It is, of course, possible that the 7 patients who did not come to autopsy had islet-cell tumors or hyperplasia, since these entities cannot be excluded without post-mortem examination. There was nothing in the clinical course of these patients to suggest such a condition, however, and it seems reasonable to assume that the hypoglycemia was due to liver disease because of the known association with hepatic impairment and the complete absence of factors indicating another diagnosis. Cases 1 and 15 never had symptoms of hypoglycemia until typical viral hepatitis developed, and the hypoglycemia was present only in association with activity of the liver disease. Case 4 was explored surgically and proved by biopsy to have an adenocarcinoma of the pancreas and biliary cirrhosis; there was no evidence of an islet-cell tumor. Case 7 was also explored surgically, cirrhosis of the liver and chronic pancreatitis being found. Cases 6, 12 and 13 had isolated episodes of hypoglycemia associated with obvious clinical liver disease, which was due to alcoholic cirrhosis in Cases 6 and 13 and to chronic passive congestion of the liver secondary to constrictive pericarditis in Case 12. All 3 of these patients have been followed for many years since the hypoglycemia was discovered, and with improved liver function no further episodes of hypoglycemia have appeared.

The mechanism of hepatic hypoglycemia is not entirely clear. Disturbances of any of the following three recognized functions of the liver may contribute to the development of hypoglycemia: glycogenesis, glycogenolysis and gluconeogenesis.[3] If the liver is unable to store glycogen, the blood sugar may fall during periods of fasting. Similarly, inability of the liver to break down glycogen, as in Von Gierke's disease,[4] may produce hypoglycemia. Possibly of equal importance is the liver's ability to produce glucose from noncarbohydrate precursors.

It is interesting to note in Table 2 the occurrence of hypoglycemia in liver disease of such varying causes. As might have been anticipated, types of liver injury widely different pathogenetically produced the same functional defect.

In some cases the extent of hepatic damage was clinically obvious, the patients having outspoken signs and symptoms of advanced liver disease. In others, however, there was little clinical evidence of liver disease, or the findings indicated a degree of hepatic impairment considered unimportant. Indeed, there were occasions when the development of spontaneous hypoglycemia first suggested the presence of significant liver damage.

Hypoglycemia may appear as liver damage progresses, or it may occur episodically in patients with a more or less stabilized degree of hepatic insufficiency, during periods of sudden stress. Such a stress may result from an alcoholic debauch, an acute infection or an operative procedure. Why these isolated episodes of hypoglycemia occur is not clear. The patient's general condition may otherwise remain unaltered.

In mild form, hepatic hypoglycemia may produce nervousness, increased sweating and palpitations. In more severe states the patient may behave in a bizarre manner and be considered psychotic, or may have convulsions or enter a state of shock. It has long been recognized that there is no constant relation between the extent of depression of the blood sugar and the severity of consequent hypoglycemic manifestations. Likewise, in the cases described above, the severity of hypoglycemic episodes could not be related to the clinically apparent degree of liver impairment. In some patients who were not considered on clinical grounds to have an important amount of hepatic insufficiency profound evidence of hypoglycemia developed. This enigma was no doubt due in part to the difficulties inherent in assaying by clinical methods the extent of liver damage.

In most of the cases reported above, the real nature of the hypoglycemic episodes was not immediately recognized, thereby emphasizing the difficulty in diagnosis. This is in no small part due to the lack of awareness of many observers that hypoglycemia is not uncommonly caused by liver disease of many sorts. Again, the manifestations of hypoglycemia are nonspecific, and may be confused with other causes of disordered behavior. An important consideration is the fact that a hypoglycemic episode may occur in a complicated setting in which other manifestations of disease, such as cardiac failure, are so prominent that the evidences of hypoglycemia are completely overshadowed or misinterpreted. Finally, as already stressed, hypoglycemia due to hepatic insufficiency may occur at a time when the usual features of extensive liver damage are not clinically apparent, making recognition of the etiologic relation most difficult. Hepatic hypoglycemia will be detected when the observer is aware of its potential occurrence in any circumstance in which liver function is impaired, though perhaps unobtrusively, and at times when other manifestations of the underlying pathologic process are more prominent.

The 5 patients in whom hypoglycemia developed during the course of congestive heart failure deserve particular attention. Hepatic hypoglycemia occurring as a complication of congestive heart failure has not hitherto been emphasized. The important implications of such an occurrence are obvious. Chronic passive congestion of the liver of long standing was the underlying process in all cases. Loss of appetite and inadequate food intake, which are common in pronounced cardiac failure, perhaps contributed to the development of the hypoglycemic episodes. In the light of our experience the frequency with which hepatic congestion and inadequate diets occur during the progress of chronic cardiac failure suggests that hepatic hypoglycemia is a much more common occurrence in chronic cardiac failure than has previously been recognized. It may be especially difficult to detect the existence of hypoglycemia during the course of congestive heart failure. Usually, such patients have had no frank hepatic insufficiency, and the observer's attention is centered upon the more dramatic signs of cardiac abnormality. Any indications of disordered liver function that are present may be obscured by the complexities of the immediate cardiac problem. When palpitations, sweating and unusual behavior resulting from hypoglycemia are observed, they may readily be dismissed as manifestations of heart failure. Cerebral anoxemia may of itself produce altered consciousness or coma. But to assume that these changes are always due to anoxemia alone may preclude simple and effective therapy. Detection and correction of hypoglycemia, therefore, ranks with other essential measures employed in the management of congestive heart failure.

There are few, if any, contraindications to the intravenous administration of small volumes of concentrated glucose, and this simple test will usually effect dramatic and diagnostic improvement if hypoglycemia is the cause of mental clouding or coma. It is wise, however, if possible, to draw blood for a sugar determination before the glucose is injected. If hypoglycemia has been present for a long time, there may be persistent mental damage that will not readily respond to administration of glucose. Sometimes, indeed, prolonged hypoglycemia may produce irreversible cerebral damage.

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THE TREATMENT OF WRINGER-ARM INJURIES*

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BOSTON

The term, "wringer arm," was first coined in 1938§ to describe an accident occurring in early childhood in which the upper extremity is inadvertently caught between the rollers of a power-driven washing-machine wringer. In addition to 26 cases previously reported, 116 children with this injury have been treated at the Children's Medical Center, Boston, from 1937 through 1951. In recent years there seems to have been a marked decrease in the incidence of this type of accident, probably owing to the perfection of emergency-release devices on automatic wringer machines and to the wider use of machines equipped with a centrifugal spin-drier mechanism. However, as long as power-driven roller wringers are used in households, wringer-arm injuries will continue to occur. Therefore, a summary of the methods of treatment that have proved successful in the handling of these children may be of interest to the physician or surgeon who is called upon to treat such patients.

Often, this injury occurs during the first week's possession of the machine, for it is at this time that the child is most fascinated by the turning rollers, and the mother is least aware of the potential dangers. There are several factors that influence the severity of the injury. Less damage will be incurred if the mother remains calm and simply strikes the safety-release bar. Too often, she follows her natural impulse to apply counter traction to the child, or to reverse the direction of the rollers, thereby subjecting the arm to a second crushing. The injury will be less severe if the child is very young, since the arm is smaller and the tissues are more yielding. The injury will be more severe if the setting of the rollers is tight, or if the arm is imprisoned between the rollers for any appreciable time. Usually, the axilla or the supracondylar region is the most severely affected, for it is in these areas that the rollers churn about for the longest period.

Because the experience is terrifying to both the parent and child, over 80 per cent of patients were

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§MacCollum, D. W. Wringer arm. *New Eng. J. Med.* 218:549-554, 1938.