The iron loss in these 50 individuals with supposedly normal menstrual periods varied from 3.84 to 78.4 mg. per period. This represents from 1.146 to 23.403 gm. of hemoglobin. If this is expressed in terms of cubic centimeters of blood, calculated in each instance from the patient's own hemoglobin content in grams per 100 cc., it represents a loss of 9.39 to 207.28 cc. with a mean of 36.7 cc. of blood per menstrual period. Much larger amounts of iron and hemoglobin were lost by the patients with hypochromic anemia even though they considered their menstrual periods to be entirely normal.

The loss of 78.4 mg. of iron at each menstrual period would necessitate a daily iron retention of approximately 2.8 mg. to replace that lost by menstruation alone. The results of iron balance studies, which are to be reported later, suggest that such a high iron retention is distinctly unusual with the average dietary intake of iron. This may explain the development of certain cases of idiopathic hypochromic anemia.

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Effect of Low Carbohydrate Diet on Glucose Tolerance in Spontaneous Hypoglycemia.

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Since it was first pointed out by Gibson[1] that hypoglycemic symptoms not artificially produced may constitute a definite clinical entity, there has arisen considerable controversy as to the treatment of spontaneous hypoglycemia (or "hyperinsulinism"). Such views are that medical therapy is valueless and that relief of symptoms can be obtained only by surgical removal of a portion of the pancreas (or tumor of the pancreas[2]), frequent feedings of carbohydrates are indicated,[3] and that the diet should be low in carbohydrate and high in fat.[4] One investigator has suggested the use of insulin

[1] Gibson, R. B., and Larimer, R. N., *J. Am. Med. Assn.*, 1924, **82**, 468.

[2] Wilder, R. M., *International Clin.*, 1933, **2**, 1.

[3] Gammon, G. D., and Tenery, W. C., *Arch. Int. Med.*, 1931, **47**, 829.

[4] Harris, Seale, *J. Am. Med. Assn.*, 1933, **101**, 1958.

to diminish the glucose tolerance[5] which was observed to occur in insulinized non-diabetic patients by Paul, Clark, and Gibson.[6]

This communication reports the diminution of glucose tolerance and the relief of symptoms in 2 cases of mild to moderately severe spontaneous hypoglycemia with a low carbohydrate high fat diet.

TABLE I.
Effect of Low Carbohydrate Diet on the Glucose Tolerance in Spontaneous Hypoglycemia.

Case 1. P.H.			Case 2. F.F.		
Time	Blood Sugar	Remarks	Time	Blood Sugar	Remarks
10-24-32		Mild symptoms	10-4-32		
8:00	66	50 gm. glucose	5:00		50 gm. glucose
8:30	150		8:00	75	50 " "
9:00	159		8:30	118	
9:30	124		9:00	173	
10:00	98		9:30	147	
10:30	55	Hunger, weakness	10:00	73	
10:45		50 gm. glucose	10:30	37	Severe symptoms
11:00	131	Symptoms disap.	11:00	55	
11:30	129		11:30	59	Symptoms milder
12:00	118		3-17-33	Patient on high fat diet since 10-4-32	
12:30	52	Severe symptoms			
1:00	55		8:00	78	50 gm. glucose
1:30	71	Symptoms milder	8:30	189	
1:45		10 gm. glucose	9:00	226	
2:00	95	Symptoms cleared	9:30	217	
Put on high fat diet 10-24-32			10:00	189	
10-11-33			10:30	170	
8:00	124	50 gm. glucose	11:00	140	50 " "
8:30	189		11:30	124	
9:00	204		12:00	204	
9:30	179		12:30	200	
10:00	138		1:00	170	
10:30	78	Severe hunger	1:30	142	No symptoms during test
10:45		50 gm. glucose			
11:00	114				
11:30	170				
12:00	155				
12:30	104				
1:00	79	Slight hunger			
1:30	77	Tremor			
2:00	95	Feeling better			
High fat diet plus 3 slices bread since 10-11-33					
10-18-34					
8:00	112	50 gm. glucose			
8:30	189				
9:00	221				
9:30	157				
10:00	109				
10:30	78				
11:00	72	Slight hunger and tremor			
11:30	82	Feeling better			

[5] John, H. J., *Endocrinology*, 1933, **17**, 583.

[6] Paul, W. D., Clark, B. B., and Gibson, R. B., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 353.

The clinical diagnosis and progress of these cases were confirmed by use of the double glucose tolerance test described by Hamman and Hirschman.[7] Blood sugars[8] were obtained every 30 minutes during the test. Two 50 gm. glucose meals were given 2¾ to 3 hours apart. The detailed account of these experiments is given in the following protocols, and the effect of the diet upon the glucose tolerance curves is summarized in Table I.

Case 1. A white male, aged 32, entered the University Hospital on 10-21-32. The symptoms were of 5 years' duration and consisted of attacks of heart palpitation which were preceded by nervousness, weakness, apprehension, shaking, perspiration and extreme hunger, occurring usually 2 to 3 hours after meals. The symptoms persisted in spite of treatment for heart disease and even after thyroidectomy. The physical examination was essentially negative. The basal metabolism was plus 14%.

The symptoms decreased after the patient had followed a daily diet of protein 60 gm., carbohydrate 60 gm., and fat 210 gm. for one year, and it will be noted from Table I that the glucose tolerance decreased. The maximum and minimum blood sugars on 10-21-32 were 159 and 52 mg. respectively, while on 10-11-33, one year later, they were 204 and 77 mg. The glucose tolerance and symptoms were practically unchanged after 3 slices of bread had been added to the diet. The patient reported on May 7, 1935, after 7 months on a general diet, that the frequency and severity of the previous attacks were again evident, particularly after a meal rich in carbohydrates.

Case 2. A white male, aged 48, entered the hospital on 9-29-32; had had attacks of weakness and jaundice at 3 to 4 month intervals for 6 years. The attacks of jaundice had gradually decreased while those of weakness had increased in frequency and severity. The weakness usually occurred 2 to 3 hours after meals and was accompanied by dizziness, but there was no history of perspiration, hunger or nervousness. The physical examination and laboratory findings revealed nothing of significance. The glucose tolerance, 5 days after admission, was increased with a minimum blood sugar of 37 mg. A daily diet of protein 60 gm., carbohydrate 60 gm., and fat 210 gm. was followed for 5 months with complete relief of symptoms and a marked diminution in glucose tolerance. The minimum blood sugar on 3-17-33 was the fasting one of 78

[7] Hamman, L., and Hirschman, I. I., *Bull. Johns Hopkins Hosp.*, 1919, **30**, 306.

[8] Gibson, R. B., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 480.

mg. and the maximum 226 mg. one hour after the first 50 gm. of glucose.

The etiology of spontaneous hypoglycemia has been generally regarded as an over production of insulin, and while in a few cases tumors of the pancreas have been demonstrated,[9] other cases have shown normal pancreatic tissue.[10] Other possible causes of hypoglycemia should not be ignored. Experimental work has demonstrated hypophysectomized animals are very susceptible to spontaneous hypoglycemia[11] and to a less extent adrenalectomized animals.[12] The liver itself may be the controlling factor both physiologically[13] and pathologically.[14]

The medical treatment of hyperinsulinism with low carbohydrate high fat diets seems very rational. The decrease in glucose tolerance on such a diet was first shown by Sweeney[15] and verified by many workers; the experiments reported here show it clearly. That high carbohydrate or repeated ingestion of glucose under appropriate conditions stimulate the glucose tolerance has been shown in normals by Hamman and Hirschman[7] and others, and in diabetics by Gibson[16] as well as by others. It would seem logical then to expect that cases of hyperinsulinism would show a reduction of glucose tolerance and relief of symptoms by the use of a low carbohydrate diet, while certain other cases of spontaneous hypoglycemia may not respond to such treatment.

Summary. The marked improvement in symptoms and glucose tolerance curves in 2 cases of spontaneous hypoglycemia (hyperinsulinism) are reported following diets high in fat and low in carbohydrate.

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9 Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E., *J. Am. Med. Assn.*, 1927, **89**, 348.

10 Finney, J. M. T., and Finney, J. M. T., Jr., *Ann. Surg.*, 1928, **88**, 584.

11 Houssay, B. A., and Biasotti, A., *Endocrinology*, 1931, **15**, 511.

12 Barnes, B. O., Scott, V. B., Ferrill, H. W., and Rogoff, J. M., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 524.

13 Soskin, S., Allweiss, M. D., and Cohn, D. J., *Am. J. Physiol.*, 1934, **109**, 155.

14 Best, C. H., Ferguson, G. C., and Hershey, J. M., *J. Physiol.*, 1933, **79**, 94.

15 Sweeney, J. S., *Arch. Int. Med.*, 1927, **40**, 818.

16 Gibson, R. B., PROC. SOC. EXP. BIOL. AND MED., 1929, **26**, 449; *J. Lab. and Clin. Med.*, 1929, **14**, 597.