The Effects of Supplementary Calories on Nitrogen Storage at High Intakes of Protein in Patients with Chronic Liver Disease

By IRVIN C. PLOUGH,* FRANK L. IBER,† MARGARET E. SHIPMAN,‡ AND THOMAS C. CHALMERS §

A DIET RICH in protein has an established place in the treatment of cirrhosis of the liver.[1] Successful therapy is accompanied not only by the return of altered liver function tests toward normal, but also by restoration of depleted protein tissue. Of the latter changes, the rebuilding of wasted musculature is perhaps the most obvious sign. The measurement of overall changes in body protein is best accomplished in short-term studies by determination of the nitrogen balance. The attainment of a large positive balance may thus reflect improvement in a patient with cirrhosis, although the liver function tests may be relatively static.

It has recently been observed that dietary nitrogenous constituents are not always beneficial in patients with severe liver disease. A high level of dietary protein may sometimes, in fact, initiate hepatic coma.[2] Impending coma thus produced can occasionally be reversed by reduction of the dietary nitrogen intake. Such reduction is accompanied by decreased nitrogen retention as measured by the nitrogen balance technique.

It might be possible to maintain a large positive balance of nitrogen in such patients at a lower, safer level of dietary protein intake by taking advantage of the protein-sparing effect of extra carbohydrate or fat calories. The present study was designed to measure the amount of nitrogen spared by large supplements of carbohydrate or fat in three patients with liver disease receiving adequate diets supplying moderate to large amounts of protein.

From the Department of Metabolism, Medical Division, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington 12, D. C.

* Major, MC, U. S. Army.

† 1st Lt., MC, U. S Army.

‡ 1st Lt., WMSC, U. S. Army.

§ Capt., MC, U. S. Army.

METHODS AND PATIENTS

The subjects of the present study were three men suffering from chronic liver disease. Patient 1 had severe cirrhosis with ascites; patient 2 had mild asymptomatic cirrhosis. The diagnosis in patient 3 was portal vein thrombosis. Case summaries are given below.

Patient 1 was a 44-year-old white Army corporal who was hospitalized for progressive abdominal enlargement six months before study. He had imbibed liberally of beer and whiskey for 12 years and at the time of admission had massive ascites, spider angiomata, splenomegaly and a palpable liver. The serum albumin was 2.7 g and the total protein was 6.8 g per 100 ml. The sulfobromophthalein retention was 40 per cent. A roentgenogram after a barium swallow revealed varices of the lower one-third of the esophagus. The patient was treated with a low salt diet and occasional mercurial diuretics which controlled the ascites in the subsequent year.

Patient 2 was a 36-year-old white mess sergeant who became ill in December 1953 with nausea, vomiting, and anorexia, followed shortly by jaundice. The diagnosis of infectious hepatitis was made. He improved in the subsequent six months on conservative therapy but abnormal sulfobromophthalein retention persisted and the liver remained enlarged. He drank five to six bottles of beer weekly. At the time of study, ten months after onset of the illness, the liver was palpable 6 cm beneath the costal margin, the spleen was not palpable, but spider angiomata were present. The total protein was 8.2 g per 100 ml, the albumin 3.6 g, and there was 12 per cent retention of sulfobromophthalein dye. Liver biopsy showed distortion of the lobular architecture.

Patient 3 was a 23-year-old white airman who first noted anorexia, malaise, and jaundice in June 1953 and was found on examination to have a tender liver and splenomegaly. All symptoms suggesting hepatitis subsided, but splenomegaly persisted. Esophageal varices were present and repeated sulfobromophthalein tests showed retention of 10 to 16 per cent of the dye. Three liver biopsies showed only slight periportal scarring. Fourteen months after onset a laparotomy revealed extrahepatic portal vein thrombosis and a splenorenal shunt was performed. Three months after the shunt the esophageal varices appeared to be unchanged, but the pressure had diminished.

Nitrogen balance experiments generally took the following form: After a control period on a diet containing sufficient protein and calories to maintain positive nitrogen balance and a reasonably constant body weight, the diet was increased by 1000 calories of fat. In the following period carbohydrate was substituted isocalorically for the fat. In the last period the patients again received the control maintenance diet. The effects of carbohydrate or fat, or both, were studied in each patient at two or more levels of dietary protein. When the protein intake was raised the intake of non-protein calories was also increased by an amount equal to 50 per cent of the increment of protein calories to cover the specific dynamic action of protein. Potassium and sodium balances were also measured in four of the eight studies.

Throughout the experiments the patients were kept on a metabolic ward. Urine was collected under refrigeration for one- or two-day periods; stools for from two- to ten-day periods. Liquid diets of constant composition were employed. The main source of protein for patient 1, whose dietary sodium had to be restricted, was dialyzed milk protein*, for the other two patients skim milk powder was used. The carbohydrate sources were primarily lactose and sucrose; the fats used were butter and vegetable oil emulsion. Potassium was added to provide at least 150 meq per day. Each patient received a standard multivitamin preparation daily. All urine and stool collections, and weekly diet aliquots were analyzed for nitrogen by the macro-Kjeldahl method, and for potassium and sodium by flame photometry. Stool fat was measured in patients 1 and 2. In calculating the average balances during a particular period, the early days in a study period before steady excretion was reached were omitted. In the periods of caloric supplementation only the first two, or at most four, days were discarded. In measuring the effect of a supplement, the balance in the experimental period was compared with the average balance of both the pre- and postexperimental control periods.

In patient 2, skin-fold thickness was measured by the method of Brožek and Keys,[3] and body specific gravity was determined by underwater weighing.[4] Body fat was calculated by the formula of Rathbun and Pace.[5] Theoretical weights were calculated as follows: Each daily balance was corrected for the average balance in the initial control period, and the daily balances were accumulated. The cumulative balance of nitrogen multiplied by 32 is the theoretical weight change based on nitrogen (lean tissue), and the cumulative balance of sodium multiplied by 7.14 is the theoretical weight change based on sodium (extracellular fluid).[6]

Selected nitrogen balance data have been included here from eight patients, studied in this department for other reasons, in whom large changes of caloric intake were made without change in protein intake. *Patient 4* had moderately severe cirrhosis; *patient 5* was essentially normal. (Patients 4 and 5 are the same patients as P. S. and T. K. in Reference 7.) *Patients 6 through 11*, who were underweight, were in late convalescence from severe injuries. (They are the same as patients 3, 6, 7, 10, 12, and 13, respectively, in Reference 8.)

RESULTS

There was no evidence of any change in the clinical state of any of the patients that could be attributed to the experimental procedures. The liquid diets, both the maintenance diets and those supplemented with large amounts of carbohydrate or fat, were well tolerated. The high fat diets caused no gastrointestinal symptoms.

* Largely Casec®, supplied by Mead Johnson and Company, Evansville, Indiana.

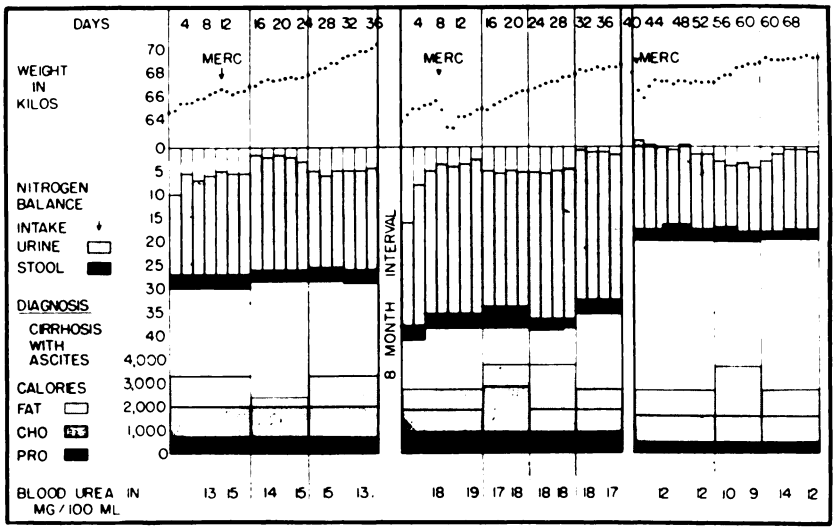

Fig. 1. Balance data from patient 1.

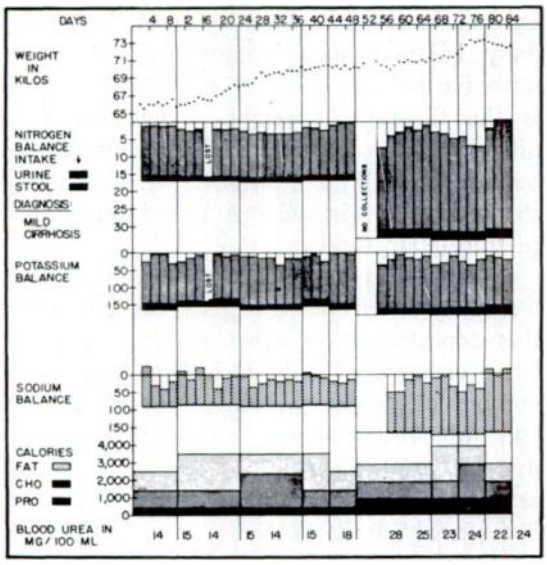

Fig. 2. Balance data from patient 2.

The caloric supplements spared nitrogen in every experiment (Figs. 1–3). The nitrogen spared, expressed as milligrams of nitrogen spared per added calorie, varied from 1.4 to 6.5 (Table I). Fat spared 1.4 to 4.0, and carbohydrate 1.4 to 6.5 milligrams of nitrogen per added calorie. In patients 1 and 3 the nitrogen spared by fat and by carbohydrate was approximately the same, but in patient 2 carbohydrate spared nearly twice as much nitrogen as did fat at both levels of nitrogen intake. In this patient, and also in patient 1, there were no significant differences in stool fat in the control, fat, or carbohydrate periods.

Potassium balances paralleled those of nitrogen, the ratio of potassium to nitrogen varying in the range of 4 to 8 meq per gram. In patient 2, the sodium balance was less positive than the control balance when the fat supplement was fed, more positive when the supplement was carbohydrate. No consistent change in sodium balance was noted in patient 3.

The amount of nitrogen spared by the supplements seemed to be directly related to the level of dietary protein intake. To confirm this point additional data were obtained in eight patients from studies done for other purposes in this department. In Figure 4 the nitrogen spared in milligrams per added calorie of fat, carbohydrate, or both, is plotted as a function of dietary protein intake in grams per kilogram of body weight, including eighteen studies on the combined eleven patients. It is apparent on inspection that good correlation exists. The correlation coefficient is 0.73, with a probability of less than 0.01. The formula for the regression line is $Y = 0.19 + 1.05X$.

DISCUSSION

The range of nitrogen sparing found in these three patients with liver disease, 1.4 to 6.5 milligrams of nitrogen per added calorie, is

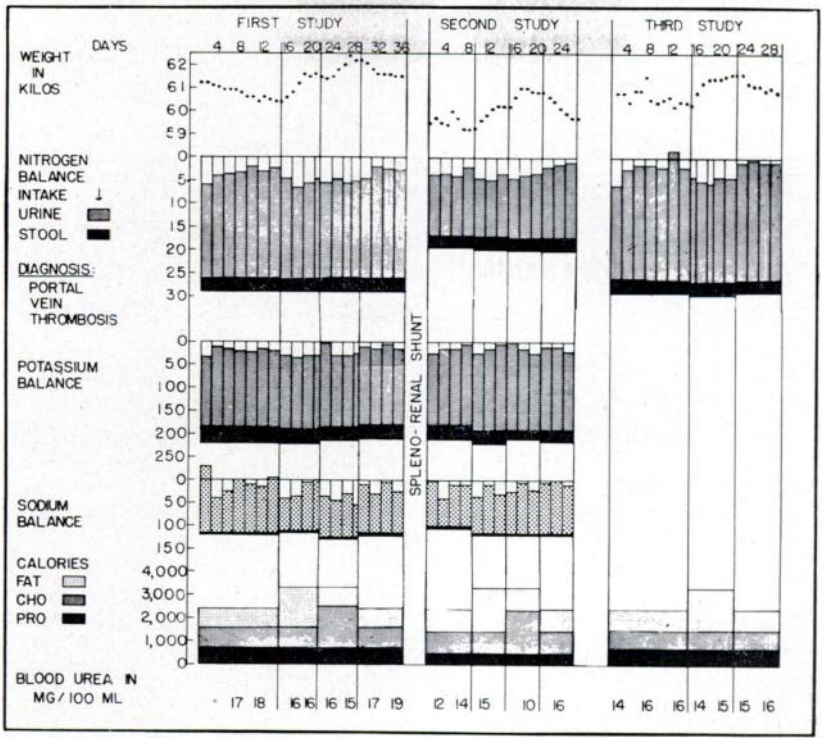

Fig. 3. Balance data from patient 3.

slightly higher than that listed in Munro's review,[9] where the range was 0.4 to 3.9, with a mean of 1.8, in experiments on man. From the present limited experience, it would appear that caloric supplements can spare nitrogen as well in patients with liver disease as in normal individuals. Therefore, if a high level of nitrogen storage is considered desirable in the treatment of chronic liver disease, large supplements of fat or carbohydrate can take the place of a certain amount of dietary protein in those patients to whom a high protein diet may be harmful.

The increase in the magnitude of the protein-sparing effect of added calories with increase in the level of dietary protein has not previously been reported. This relation may be a partial explanation for the variations in the figures collected by Munro.[9] The small protein-sparing effect seen in an individual receiving a low protein diet may be explained as follows: An irreducible minimum certainly exists in nitrogen excretion. When an individual's nitrogen intake is reduced to this level or less while his energy requirement is provided, extra calories could not affect his nitrogen balance. The explanation of the continued increase in nitrogen sparing with increasing protein intakes must await a general elucidation of the mechanism of nitrogen sparing.

Ingested calories above the energy requirement are stored as fat. Keys and Brožek[10] point out that body fatty tissue contains supporting structure (protein, water, etc.) averaging 38 per cent by weight. Such fatty tissue would contain 1.1 per cent nitrogen. It may be calculated that for each calorie stored as fat, 1.8 milligrams of nitrogen must also be stored. As mentioned above, this is the mean value of protein spared per added calorie in Munro's compilation of data from man. Although the hypothesis that the nitrogen-sparing effect of surfeit carbohydrate represents the formation of fatty tissue[7] is a reasonable one, it cannot be considered complete in view of the finding that the magnitude of nitrogen sparing depends on the level of protein intake. Indeed, values of 5 milligrams of nitrogen spared per added calorie (Fig. 4) are consistent with the formation of lean body

TABLE I

Changes in Nitrogen Balance Produced by Large Supplements of Carbohydrate or Fat Added to a Maintenance Diet

Patient and study	Maintenance diet		Caloric supplement		Nitrogen balance			Mg N spared per added calorie		
	Protein	Calories per kg	Calories	Type	Pre-control period	Experimental period	Post-control period	Fat	CHO	Both
	g/kg				g/day	g/day	g/day			
1A	3.0	40	900	Fat	—	5.4	2.1	3.5	—	—
					2.1	5.1	—			
B	4.0	45	1000	CHO	3.3	5.3	—	2.8	3.0	3.0
			1000	Fat	—	5.1	1.2			
C	2.0	45	1000	Fat	0.7	4.0	1.0	3.2	—	—
2A	1.5	37	1000	Fat	1.0	2.0	—	1.4	2.8	2.1
			1000	CHO	—	3.4	—			
			1000	Fat	—	2.0	0.1			
B	3.0	41	1000	Fat	1.6	4.2	—	3.6	6.5	5.0
			1000	CHO	—	7.2	−0.4			
3A	3.0	40	900	Fat	2.8	5.7	—	3.3	2.7	3.0
			900	CHO	—	5.1	2.6			
B	2.0	40	900	Fat	3.6	3.8	—	1.9	1.4	1.7
			900	CHO	—	3.4	0.6			
C	3.0	40	900	Fat	0.8	4.3	0.7	4.0	—	—
4	1.0	21	1000	CHO	2.1	3.5	—	—	1.4	—
5	1.2	36	1000	CHO	1.3	2.3	—	—	2.2	—
					—	2.8	−0.8			
6	1.8	47	1000	Both	3.9	4.6	1.5	—	—	1.9
7	2.0	50	700	Both	—	5.4	4.2	—	—	1.7
8A	2.2	47	800	Both	5.3	6.8	—	—	—	1.9
					—	2.6	1.1			
B	1.6	43	1000	CHO	2.2	4.1	—	—	1.2	—
					—	5.4	4.8			
9	1.7	50	1000	CHO	1.9	3.8	—	—	1.9	—
10A	1.0	40	1000	Both	1.6	2.9	2.1	—	—	1.0
B	2.0	29	1000	Both	2.7	6.2	—	—	—	3.5
11	1.1	37	1000	Both	2.1	2.2	—	—	—	0.1

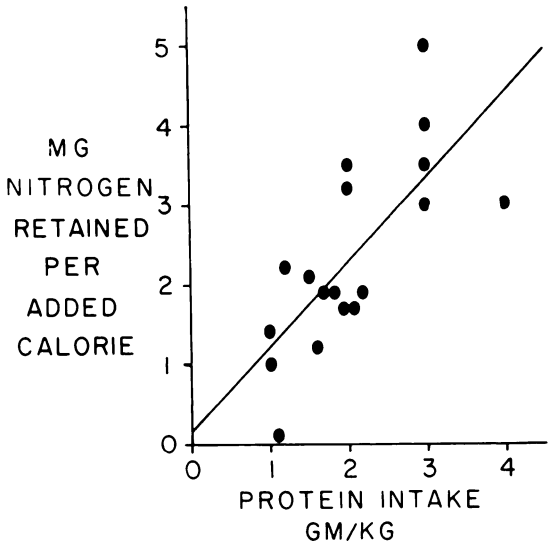

Fig. 4. Milligrams of nitrogen spared per added calorie as a function of dietary protein intake in grams per kilogram of body weight.

tissue which contains approximately 5 per cent nitrogen.

A series of calculations were performed to seek collateral evidence of the type of body tissue, fat or lean, formed in response to surfeit feeding. The ratios of nitrogen spared to weight gained were determined in each of the studies in Table I, but these ratios were highly variable, and so shed no light on the problem. In patients 2 and 3, the availability of balance figures for both nitrogen and sodium permitted the calculation of the theoretical weight changes from nitrogen (lean tissue) and from sodium (extracellular fluid). The theoretical weight changes from nitrogen and from both nitrogen and sodium are compared with observed weight changes in Figure 5. The difference between the observed weight change and the theoretical weight based on both nitrogen and

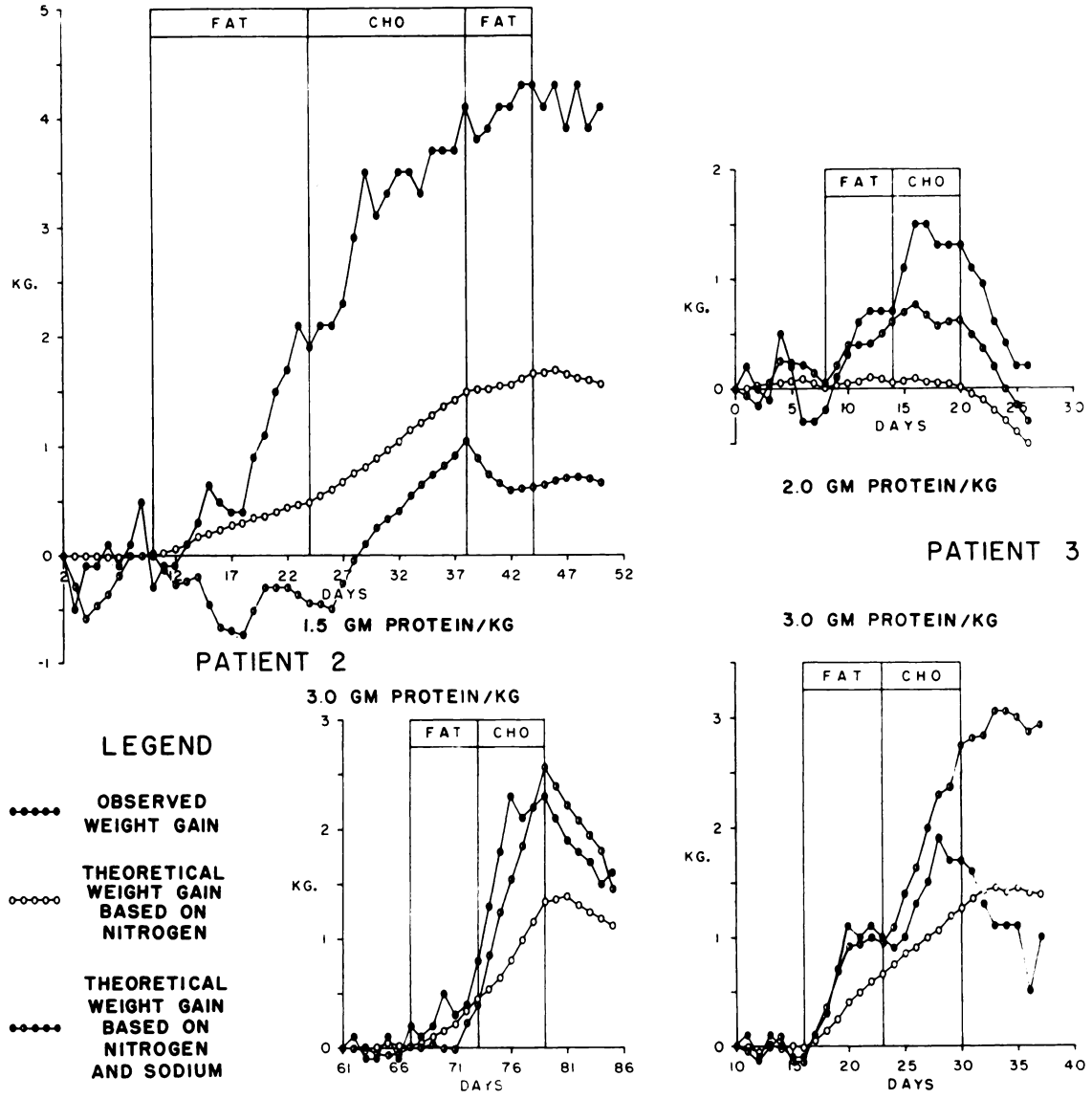

Fig. 5. Observed and theoretical weight changes during the studies in patients 2 and 3.

sodium may be considered to represent the change in body fat.

Examination of Figure 5 suggests that at the higher protein intake the weight gain is accounted for by gains in lean tissue and extracellular fluid, without increase in body fat; in fact, patient 3 may have lost fat in the after-control period. On the lower protein intake, patient 2 would seem to have gained mainly fat, patient 3 both lean tissue and fat.

In patient 2, attempts were made to follow changes in body fat both by measurement of skin-fold thickness and by densitometry. The former method indicated a gain of 1.5 kg of fat during the study on the lower protein diet, less than a third of the gain calculated from the balances. At the higher protein intake, the skin-fold measurements indicated a gain of 1 kg of fat, although the balance data suggested no change. Although densitometry, on the other hand, indicated a slight loss of body fat in both studies, these results should be discarded, since the small changes in specific gravity probably do not exceed the error of the method. The skin-fold thickness measurements, however, were consistent.

SUMMARY AND CONCLUSIONS

In three patients with liver disease large supplements of carbohydrate or fat spared amounts of nitrogen varying from 1.4 to 6.5 milligrams per added calorie. In two patients the effects of carbohydrate and fat were equal; in the third patient carbohydrate was twice as effective as fat.

The amount of nitrogen spared per added calorie was directly related to the level of protein in the diet. It is suggested that at lower protein intakes an excess of calories leads to the formation of fat, but at higher protein levels leads to the formation of lean tissue.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Richard Meyer, Department of Medicine, Georgetown University Medical School, and the personnel of the Experimental Diving Unit, Naval Gun Factory, Washington, D. C., for the measurement of body specific gravity; Capt. Johnnie Long, ANC, U. S. Army, for patient supervision and nursing care; and the laboratory staff of the Department of Metabolism, particularly George Washington, Anna Marie Link, and Betty Hackley, for the chemical analyses. We are indebted to Dr. Bruce T. Forsyth for the data from patients 4 through 9, and to Dr. Morton C. Creditor for the data from patients 10 and 11.

REFERENCES

1. Patek, A J., Jr., Post, J., Ratnoff, O. D., Mankin, H., and Hillman, R. W.: Dietary treatment of cirrhosis of the liver. *J. A. M. A.* 138: 543, 1948.
2. Schwartz, R., Phillips, G. B., Seegmiller, J. E., Gabuzda, G. J., Jr., and Davidson, C. S.: Dietary protein in the genesis of hepatic coma. *New England J. Med.* 251: 685, 1954.
3. Brožek, J., and Keys, A.: The evaluation of leanness-fatness in man: norms and interrelationships. *Brit. J. Nutrition* 5: 194, 1951.
4. Behnke, A. R., Feen, B. B., and Welham, W. C.: Specific gravity of healthy men. *J. A. M. A.* 118: 495, 1942.
5. Rathbun, E. N., and Pace, N.: Studies on body composition. I. Determination of body fat by means of the body specific gravity. *J. Biol. Chem.* 158: 667, 1945.
6. Albright, F., and Reifenstein, E. C., Jr.: *The Parathyroid Glands and Metabolic Bone Disease.* The Williams and Wilkins Co., Baltimore, 1948, p. 303.
7. Forsyth, B. T., and Plough, I. C.: The protein sparing effect of carbohydrate with and without testosterone. *J. Lab. & Clin. Med.* 46: 840, 1955.
8. Forsyth, B. T., Shipman, M. E., and Plough, I. C.: The relation of nitrogen retention to nitrogen intake in adults with post-traumatic malnutrition. *J. Clin. Investigation* 34: 1653, 1955.
9. Munro, H. N.: Carbohydrate and fat as factors in protein utilization and metabolism. *Physiol. Rev.* 31: 449, 1951.
10. Keys, A., and Brožek, J.: Body fat in adult man. *Physiol. Rev.* 33: 245, 1953.