THE BASAL METABOLISM AND THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN LIVER DISEASE *

JOSEPH C. AUB, M.D. AND JAMES H. MEANS, M.D.
BOSTON

Much study of the liver has shown that it has so large a factor of safety that even when quite severely injured by disease it is still capable of performing its metabolic functions adequately. These studies have nearly all been made from the point of view of excretion, however, and but little work has been done on the speed of absorption and the utilization of foods in liver disease. With the disturbances of circulation found in cirrhosis, and the marked loss of liver tissue, it seems reasonable that, at least, the speed of utilization of foodstuffs might be delayed. This can best be studied by the respiratory metabolism, and in this paper, therefore, the question of total metabolism and of utilization of protein in liver disease is discussed.

The specific dynamic action of protein is a term first given by Rubner [1] to the increase in total heat production which follows the ingestion of large quantities of protein. Various explanations of this fact have been offered, but the work of Lusk [2] has shown that amino-acids stimulate the body cells to increased heat formation. By feeding glycocoll to a phlorhizinized dog, he showed that the breakdown and metabolism of the acids themselves is not the cause. The total caloric content of the glycocoll was recovered in the urine as glucose and urea, but there was still a distinct specific dynamic action elicited, which must have been a response of the cells of the organism. This work has been confirmed by Grafe.[3] That this stimulation was not dependent on the mass of striated muscle nor on the surface area was suggested by Aub and DuBois,[4] who studied the effect of large quantities of meat on a legless man and an achondroplastic dwarf. These subjects with normal torsos, but reduced muscle area, responded with a

* From the Medical Service of the Massachusetts General Hospital and the Medical Department of the Harvard Medical School, aided, in part, by a grant from the Proctor Fund, Harvard University.

1. Rubner, M.: Die Gesetze des Energieverbrauchs bei der Ernährung.

2. Lusk, G.: Animal Calorimetry; An Investigation into the Causes of the Specific Dynamic Action of the Foodstuffs, J. Biol. Chem. **20**:555, 1915.

3. Grafe, E.: Beiträge zur Kenntnis der Ursachen der specifisch dynamischer Wirkung der Eiweisskörper, Deutsch. Arch. f. klin. Med. **118**:1, 1915.

4. Aub, J. C., and DuBois, E. F.: The Basal Metabolism of Dwarfs and Legless men, with Observations on the Specific Dynamic Action of Protein, Arch. Int. Med. **19**:840 (June) 1917.

relatively greater increase of metabolism than did the normal controls. This suggested that the effect might be located in the viscera.

DuBois [5] also showed that the specific dynamic action of protein was normal in exophthalmic goiter and in cretinism, the rise of metabolism being normally superimposed on the abnormal basal rate. Work reported in this article confirms this observation for hyperthyroidism. These results suggest that the thyroid gland is not the seat of the dynamic action.

A third possible organ for the origin of this specific dynamic action is, of course, the liver. There is some evidence brought forward by Salaskin [6] and Jansen,[7] and better work by Loeffler [8] and Van Slyke [9] that the liver is able to transform amino-acids into urea. But Loeffler [10] has also shown that fasting livers, perfused with a nitrogen-free solution, may form urea. This makes conclusions from this type of work questionable, although Loeffler still believes that urea is formed in the liver from some amino-acids. Fiske and Sumner,[11] however, have shown that urea may be formed from amino-acids in an organism with the liver eliminated, which suggests that urea formation from amino-acids is not confined to the liver.

There has been much study of the metabolism in liver disease, from the point of view of amino-acid assimilation and excretion. Bergell and Blumenthal [12] found no reduced catabolism of amino-acids other than leucin and tyrosin in a case of acute yellow atrophy. Feigl and Luce [13] carefully studied a case of acute yellow atrophy and observed a marked negative nitrogen balance as well as an increased excretion of amino-acids in the urine. The interesting case of yellow atrophy studied by Stadie and Van Slyke [14] showed a marked increase of amino-

5. DuBois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

6. Salaskin, S.: Ueber die Bildung von Harnstoff in der Leber der Säugetheire aus Amidosäuren der Fettreihe, Ztsch. f. physiol. Chem. **25**:128, 1898.

7. Jansen, B. C. P.: The Function of the Liver in Urea Formation From Amino-Acids, J. Biol. Chem. **21**:557, 1915.

8. Loeffler, W.: Ueber Harnstoffbildung in der isolierten Warmblüterleber, Biochem. Ztschr. **76**:55, 1916.

9. Van Slyke, D. D.: Significance of the Amino-Acids in Physiology and Pathology, Arch. Int. Med. **19**:56 (Jan.) 1917.

10. Loeffler, W.: Desaminierung und Harnstoffbildung in Tierkörper, Biochem. Ztschr. **85**:230, 1918.

11. Fiske, C. H., and Sumner, J. B.: The Importance of the Liver in Urea Formation from Amino-Acids, J. Biol. Chem. **18**:285, 1914.

12. Bergell, P. and Blumenthal, F.: Ueber akute gelbe Leberatrophie. Charité Ann. **30**:19, 1906.

13. Feigl, J., and Luce, H.: Neue Untersuchungen über akute gelbe Leberatrophie, Biochem. Ztschr. **79**:162, 207, 1917.

14. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693 (May) 1920.

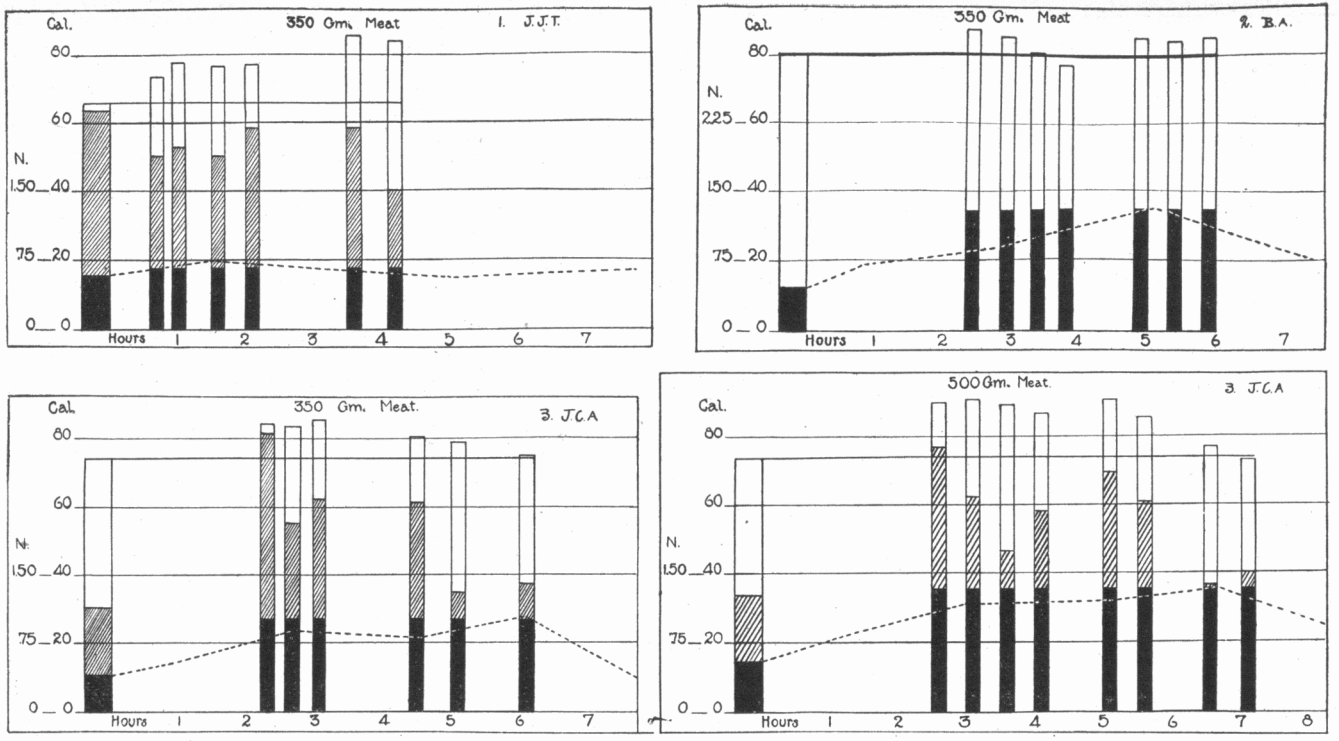

Fig. 1.—These records were made from four normal controls.

The total height of the rectangles represents the total calories metabolized per hour. The solid black areas represent the calories of protein metabolized per hour; the hatched areas represent the carbohydrate, and the unshaded areas represent the fat calories. The first observation is basal; those following are the observations taken after the ingestion of meat. The abscissa represents the time after starting the meat meal. The discontinuous line is the urinary nitrogen excretion in grams per hour. The points from which this is drawn represent the middle of the period of each urine accumulation.

acids in the urine and blood. These authors suggest that deamination and urea synthesis is incomplete without the liver, but may still occur to a considerable degree. Glaessner [15] used abnormally high amino-acid nitrogen excretion as a liver function test, but his methods were criticized by Masuda,[16] who did not get nearly as striking results in his tests. Ishihara [17] produced chronic phosphorus poisoning in the dog and found no noteworthy change in amino-acid excretion as long as the animals would eat. Levene and Van Slyke [18] found a normal amino-acid excretion in the urine of two cases of cirrhosis and in dogs poisoned with chloroform, and with chloroform and phosphorus. Marshall and Rowntree [19] observed an increase in the nitrogen in the last stages of phosphorus and chloroform poisoning in dogs, but they [20] report only slight increases in amino-acid nitrogen in both urine and blood in cases of liver insufficiency. Work along these lines, therefore, has given varying results, but the distinct impression remains that the cleavage of amino-acids is not entirely normal, though striking changes are seen only in very severe liver insufficiency.

While urinary and blood studies, therefore, have given rather conflicting results, no one, so far as we know, has studied the response of the total metabolism to protein feeding in liver disease. This is the best method, in our opinion, for studying the beginning of the utilization of ingested protein, for Lusk [2] and Csonka [21] have shown that the rise in heat production approximately parallels the speed of amino-acid metabolism, and Janney,[22] has shown that the rate of protein metabolism seems practically identical with that of amino-acids. In undertaking our experiments, therefore, it seemed reasonable that if there is a delay or an abnormal response in protein metabolism, it might be demonstrated by the respiratory exchange. Human subjects with advanced liver disease, with portal obstruction, and obstruction in the bile passages were studied. No cases of acute yellow atrophy or of

15. Glaessner, K.: Functionelle Prüfung der normalen und pathologischen Leber, Ztschr. f. exper. Path. u. Therapie **4**:336, 1907.

16. Masuda, N.: Ueber die Ausscheidung verfütterter Aminosäuren bei Leber und Stoffwechselkrankheiten, Ztschr. f. exper. Path. u. Ther. **8**:629, 1910.

17. Ishihara, H.: Ueber die Stickstoffverteilung im Hundeharne bei subchronischer Phosphorvergiftung, Biochem. Ztschr. **41**:315, 1912.

18. Levene, P. A., and Van Slyke, D. D.: Gasometric Determination of Free and Conjugated Amino-Acids in the Urine, J. Biol. Chem. **12**:301, 1912.

19. Marshall, E. K., and Rowntree, L. G.: Studies in Liver and Kidney Function in Experimental Phosphorus and Chloroform Poisoning, J. Exper. Med. **22**:333, 1915.

20. Chesney, A. M., Marshall, E. K. and Rowntree, L. G.: Studies in Liver Function, J. A. M. A. **63**:1533 (Oct. 31) 1914.

21. Csonka, F. A.: Animal Calorimetry: The Rate at Which Ingested Glycocoll and Alanine Are Metabolized, J. Biol. Chem. **20**:539, 1915.

22. Janney, N. W.: A Note on the Rate of Metabolism of Proteins and Amino-Acids, J. Biol. Chem. **22**:191, 1915.

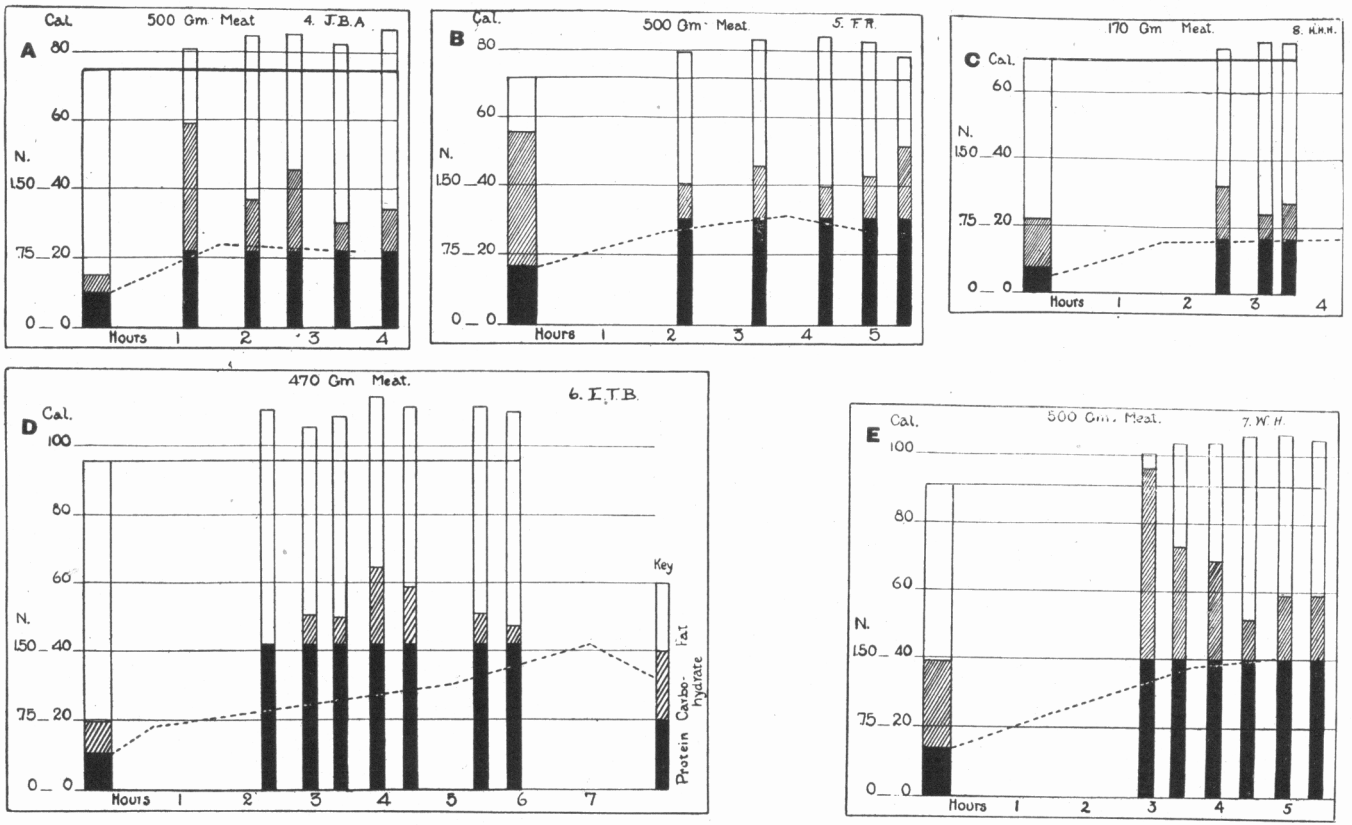

Fig. 2.—**A** and **B** are records made from normal controls. **C** was a case of carinoma probably involving the liver. **D** and **E** were cases of exophthalmic goiter.

phosphorus poisoning could be investigated. This is to be regretted, for these types of liver disease give the most striking changes in protein metabolism. Cases as uncomplicated as possible were chosen, and it was to be expected that the ability to utilize, as well as the speed of utilization, of protein foods could thus be studied. Müeller and Schultz [23] have assumed that much of the protein absorbed when there is obstruction of the portal circulation is poured into the ascitic fluid and then reabsorbed into the blood stream by way of the peritoneum. If this is true, one would expect a delay in the appearance of the dynamic action, and a reduction of its intensity. The work here reported was undertaken to study the response to protein-rich meals by patients with severe liver disease, and the results have shown that they react in an essentially normal way.

METHODS

The total metabolism was studied with a Benedict universal respiration apparatus by the methods previously described in papers from this laboratory.[24, 25] The data obtained included the oxygen absorbed and the carbon dioxid eliminated over experimental periods of about ten minutes duration. The basal figure is the average of repeated basal determinations made, usually, the day before the test meal, but the other figures in the charts are from single observations. Urinary nitrogen determinations were made by the Kjeldahl method. These analyses were made always in duplicate, usually in triplicate. The total calories used and the percentage of utilization of carbohydrate, fat and protein were calculated from the carbon dioxid and the oxygen exchange, and the nitrogen eliminated in the urine.[25] All figures and calculations have been checked carefully.

Because of the delay in nitrogen elimination, as discussed in a paper by Aub and DuBois,[4] it seemed wiser to take the maximum rate of urinary nitrogen elimination as the index of protein metabolism after meat ingestion. This was done because there is much evidence to show that the normal stimulation of metabolism by protein is at its height within two hours after eating, but that the maximum nitrogen excretion

23. Müller, L. R., and Schultz, O.: Klinische, physiologische, und pathologisch-anatomische Untersuchungen an einem Fall von hochgradigem Ascites bei Pfortaderthrombose, Deutsch, Arch. f. klin. med. **76**:544, 1903.

24. Means, J. H.: Studies on the Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **27**:121, 1915.

The case of W. K. was studied by the Tissot method at the Peter Bent Brigham Hospital. We wish to take this occasion to thank Dr. Cyrus Sturgis and Miss Edna Tompkins for making the respiratory determinations on this patient for us, and Dr. Reginald Fitz for the chemical analyses.

25. Lusk, G.: A Respiration Calorimeter for the Study of Disease, Arch. Int. Med. **15**:793 (June) 1915.

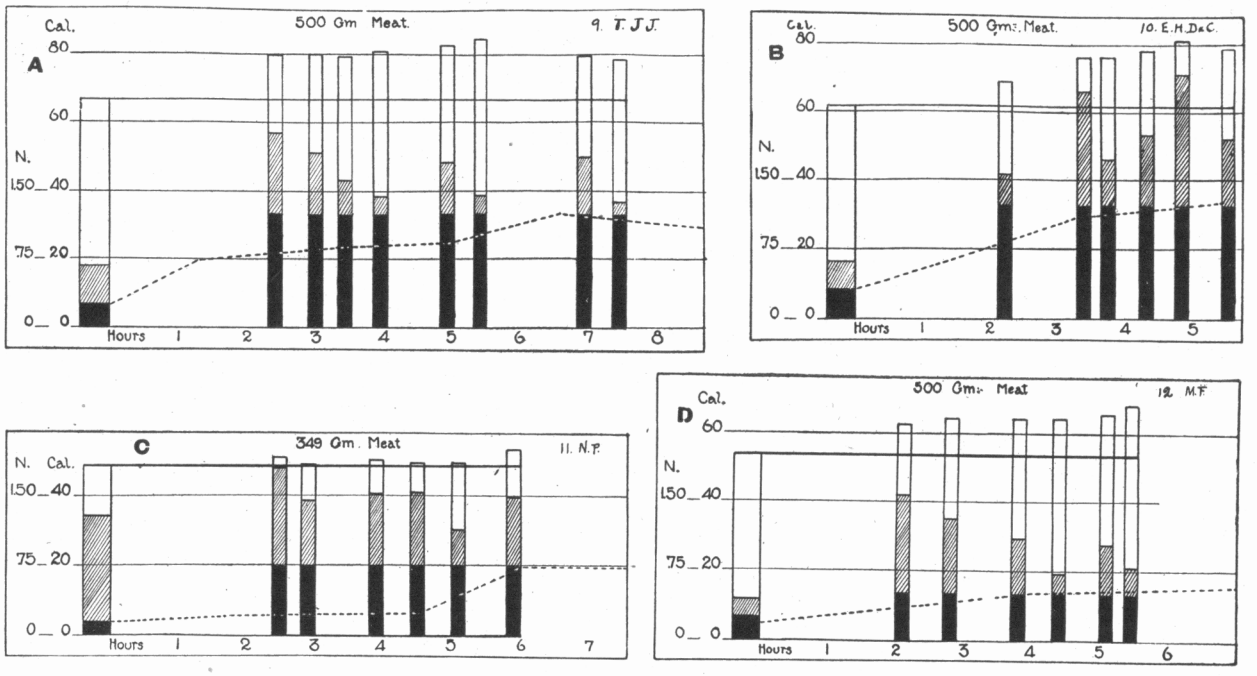

Fig. 3.—**A** and **B** are records made of two cases of obstructive jaundice. **C** was a case of gallstones. **D** was a case of cirrhosis with obstruction in which ten hours and forty minutes after eating the nitrogen curve was 0.672 gm. per hour.

may not occur for six hours after the meal.[26] When compared with the cases of Aub and DuBois, the nitrogen and the sulphur excretion in the cases of liver disease did not differ from the normal response.

With one exception, the subjects all ate, approximately either 350 or 500 gms. lean beefsteak, separated from all fat and gristle. The steak was finely chopped and cooked as meat balls, without butter. With it was served a very little stewed tomato, and water. Gigon[27] claimed that the specific action did not vary directly with the amount of protein eaten. The normal controls, however, give a direct basis of comparison for the ingestion of either 350 or 500 gms. meat.

The actual figures of our experimental data are not given in this paper, because of their very large bulk, and because we feel that the graphic presentation of the experiments while more compact is of equal value. The summary tables, however, are given.

HISTORIES

The histories of the cases studied are here given very briefly. In the hospital they were studied with great thoroughness, but only positive and pertinent findings are here recorded.

Control 1.—J. J. T. (W. S. 214,249[28]) was a young man, aged 24 years, who had had an operation for inguinal hernia ten days before study. His convalescence had been uneventful, and we, therefore, considered him normal, except that he had been bedridden.

The other controls (Nos. 2, 3, 4 and 5) were doctors and medical students working in the hospital. They were all normal men and in fair physical condition.

Two exophthalmic goiter patients were studied in relation to other work.

CASE 1.—(6) E. T. B. (E. M. and W. S. 213,101), aged 35 years, was a man with moderately severe exophthalmic goiter of six years' duration. His case is reported fully by Means and Aub[29] as Case 137, and by Means[30] as that of Mr. E. T. B.

CASE 2 (7).—W. H. (W. M. and W. S. 210,852), aged 22 years, was a man with exophthalmic goiter who was still very toxic in spite of a ligation of the superior thyroid arteries done at the Mayo Clinic. This is Case 83 of Means and Aub. He was operated on after the tests that are reported here, and one month after removal of a large part of the thyroid his metabolism was normal.

Cases of Liver Disease.—All of these patients were men except Nos. 11 and 12.

---

26. Williams, H. B., Riche, J. A. and Lusk, G.: The Metabolism of the Dog Following the Ingestion of Meat in Large Quantity. J. Biol. Chem. **12**:349, 1912.

27. Gigon, A.: Ueber den Einfluss der Nahrungsaufnahme auf den Gaswechsel, Arch. f. physiol. **140**:544, 1911.

28. All numbers following the initials of patients refer to the Massachusetts General Hospital records, except Case 16, who was a patient at the Peter Bent Brigham Hospital.

29. Means, J. H., and Aub, J. C.: The Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (May) 1919.

30. Means, J. H.: M. Clin. N. America 1099 (January) 1920.

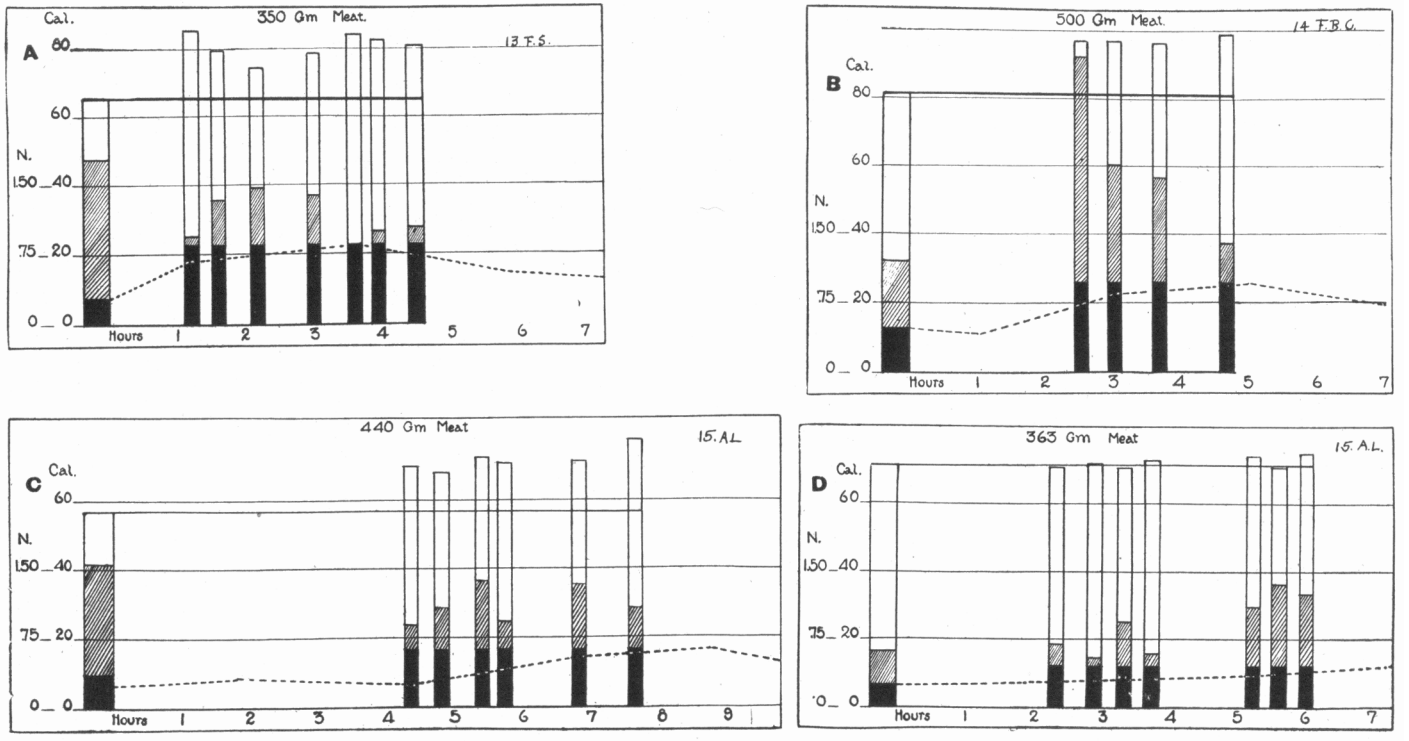

Fig. 4.—**A** was a case of early cirrhosis; **B** one of Hanot's cirrhosis; **C** and **D** was a case of cirrhosis.

CASE 3 (8).—H. H. H. (E. M. 210,905) was a married negro, aged 42. His occupation was that of restaurant chef.

For the past seven years, he had had occasional gastro-intestinal upsets with gnawing epigastric pain and nausea every few months after indiscretions in diet. They were relieved by vomiting and sodium bicarbonate. Five weeks previously these had become very frequent. Three weeks previously the pain had shifted to the right side, and a constant dull ache remained which extended into the back and occurred with deep inspiration. There were then no more gastro-intestinal symptoms. Bowels had been regular and the urine normal. He said that he had lost 13 pounds weight in the last six months. He had never been a heavy drinker.

The physical examination was negative, except for marked pyorrhea. The left pupil was larger than the right; both pupils were slightly irregular. Liver dulness extended from the fifth rib to 6½ cm. below the costal margin. The edge was sharp and tender.

Laboratory Findings.—Roentgen-ray examination showed no positive evidence of gallstones. Urinary examination showed a very slight trace of albumin, and red blood cells, a few leukocytes, and no casts in the sediment. Thirty-five per cent. phenolsulphonephthalein was excreted in two hours. No autolysis of the blood clot. The Wassermann test was strongly positive. The blood pressure was 115/70. In the specific dynamic action test, the patient could eat only 170 gm. meat, and felt that this distressed him.

He left the hospital unoperated, with the diagnosis of syphilis of the liver. He died three weeks later. His rapid death suggests a new growth rather than syphilis of the liver. No necropsy was obtained, so that the diagnosis is somewhat in doubt.

CASE 4 (9).—T. J. J. (E. M. and E. S. 213,698) was a cabinet maker, aged 51, married, who had drunk ten glasses of ale a day as well as two or three brandies a week for years. Four months before entry he had had a sharp pain on the right side of the epigastrium, radiating to the midline, which was so severe that it doubled him up. Two days later he became jaundiced. Since that time he had lost 20 pounds in weight.

Physical examination showed that the patient was very jaundiced; the liver was easily palpable 4 cm. below the costal margin, with a rounded edge, and a smooth, not tender surface.

Laboratory Findings.—Bleeding time, three minutes. No autolysis of blood clot in twenty-four hours. The stools showed a positive guaiac test twice. The gastric test meal gave a negative guaiac test. Urinary examination showed no albumin, bile + +, and many casts in the sediment. Blood pressure, 100/62.

Following our studies an operation was performed. A hard, scirrhous type of cancer was found at the junction of the cystic and common bile ducts, and there was marked backing up of thick bile. The duct and gallbladder were drained.

Diagnosis.—Carcinoma of the bile passages.

CASE 5 (10).—E. H. DeC. (E. M. 211,730) was a weaver, aged 29 years, who until shortly before entry had drunk three or four glasses of gin and from six to seven glasses of beer daily, and excessively every Saturday night. Eleven weeks before entry, a pain started in the upper abdomen which was severe at first, but which became gradually sharper and constant. For ten weeks he had had gradually increasing jaundice with six clay colored stools a day. He had lost 20 pounds in weight and was growing rapidly weaker, in spite of an excellent appetite.

Physical examination showed a very poorly nourished but well developed man, who was markedly jaundiced. His heart rate was 44 per minute. Liver dulness extended from the fourth intercostal space to 2½ cm. below the costal margin. The edge was easily felt, and was hard, smooth, slightly rounded and

not tender. The gallbladder was also palpable. The patient's weight fell in one week from 108 pounds to 99 pounds while he was in the hospital.

Laboratory Findings.—Roentgen-ray examination of the gallbladder and gastro-intestinal tract showed no definite lesion. Cardiac study showed brachycardia to be the only abnormality. Urinary examination showed the slightest possible trace of albumin, bile + + + + in two examinations, and a negative sediment. The stools showed a guaiac test + + + in four examinations. Vomitus gave a positive guaiac test. Blood pressure, 105/50.

Subsequent History.—After leaving the Massachusetts General Hospital, the patient was operated on at the Lawrence Hospital. The operation showed sarcoma of the pancreas and obstruction of the bile duct. Sarcomatous nodules later appeared on the body. The patient died at the end of January, 1917.

CASE 6 (11).—N. P. (E. M. and E. S. 311,013) a married housewife, aged 53 years, had her menopause two years before entry. Ten years before entry she had had a typical gallstone colic which had recurred several times since then, but never with jaundice. Since a typical attack, six weeks before entry, she had had dull pain.

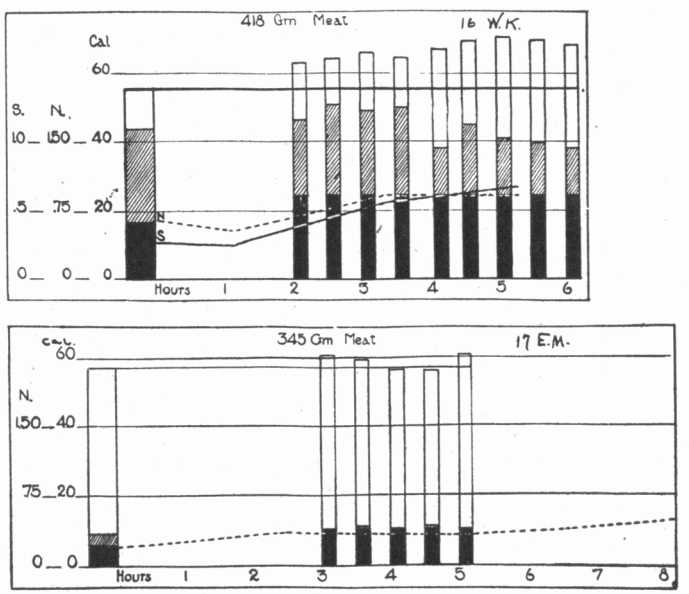

Fig. 5.—Both records were made of cases of cirrhosis. In the upper record, the curved continuous line is the sulphur execretion per hour.

Physical examination showed nothing remarkable, except that liver dulness extended from the fifth rib to 5½ cm. below the costal margin. The edge could be felt as slightly tender and sharp.

Laboratory Findings.—These were all negative, except for a positive guaiac test in the gastric contents.

Following our study Dr. F. G. Balch operated and found a thickened gallbladder with two large stones. The liver was large, dark colored, and felt granular. The pylorus was thickened, but no definite lesion was found.

Diagnosis.—Gallstones.

CASE 7 (12).—M. F. (E. M. and E. S. 212,732) was a housewife, aged 28 years. Three years before entry, after her last baby was born, she was

jaundiced for one week. Five weeks later, she had a sharp pain in mid epigastrium, with nausea, vomiting and slight jaundice. These attacks recurred very frequently. One and one-half years before entry she was operated on, and a gallbladder filled with stones was removed. The wound was drained for five weeks before healing and from that time on, fluid accumulated gradually in the abdomen. For the past ten months her abdomen had been tapped every two or three weeks. She had no pain, felt well and continued to work.

Physical examination showed that there was a slight jaundice of the sclerae; that the abdomen was very full of fluid; that there was slight edema of the legs; and that there were a few internal hemorrhoids.

The patient was tapped three times in two weeks, 17 pints of fluid being obtained each time. After tapping, the liver edge could be felt as rounded, lobulated, and hard, slightly tender, and descending on respiration.

The laboratory findings were all negative, except that the blood pressure was 105/75, and that the stools showed a faintly positive guaiac test once in four observations. The ascitic fluid showed a specific gravity of 1,016 and 1.018, 160 cells per c. mm., of which 54 per cent. were epithelial, 32 per cent. lymphocytes, and 14 per cent. neutrophils The chemical findings of the fluid were reported as Cases No. 27 and 28, Table 1, by Denis and Minot.[31]

Following our studies, Dr. Daniel Jones operated and found the liver very hard, not enlarged, lobulated, but not granular. It felt like the knuckles of the hand. The vessels of the portal system were enormously distended. There were many adhesions all over the liver and about the portal vein, and a very vascular omentopexy. The spleen was hard and large.

The patient was discharged unrelieved, with a diagnosis of cirrhosis of the liver. She died soon afterward.

While no corroboration of the diagnosis can be given, the case is very similar to those described by Hoover[32] of obstruction of the portal vein.

CASE 8 (13).—F. S. (E. M. 214,524) was a meat cutter, aged 45 years. Since he was 18 years old he had drunk one or two quarts of gin, whiskey or brandy each day, and occasionally even more. Six years before entry his abdomen had became swollen, but returned to normal size without treatment. For the past three years he had been jaundiced after unusual drinking bouts. For the last year he had felt tired and had lost about 20 pounds in weight, and occasionally he had vomited. Two months before entry, he had been jaundiced for a short period. There had been no swelling of the abdomen.

Physical examination was negative, except that the liver dulness extended from the fifth rib to 4 cm. below the costal margin; the edge was palpable.

Laboratory Findings.—No autolysis of blood clot in forty-eight hours. Poorly digested food was found in the sediment of the stools. There was no blood present. The temperature varied between 98 and 99.5 F.

The case was considered an early cirrhosis of the liver, before severe symptoms developed.

CASE 9 (14).—F. B. C. (W. M. 212,049) was an unmarried travelling salesman, 27 years. Four years before entry, he had had an attack of jaundice without other symptoms. He recovered from this in four weeks, but had always been more or less yellow ever since the attack. Two years before entry he had been acutely ill with chills, fever, malaise, jaundice and clay-colored stools, and was in a New York hospital for sixteen weeks. There he developed red, swollen joints and one knee had since that time been stiff and deformed. He had never had any other gastro-intestinal disturbances and had lost no weight.

---

31. Denis, W., and Minot, A. S.: The Nonprotein Constituents of Edema Fluids, Arch. Int. Med. **20**:879 (June) 1917.

32. Hoover, C. F.: Obstruction of the Hepatic Veins, J. A. M. A. **74**:1753 (June 26) 1920.

Physical examination showed marked jaundice. The abdomen was full, tympanitic, and was held so rigidly that the liver edge could not be felt. Liver dulness extended from the third costal interspace to 2 cm. below the costal margin. The right wrist and left knee had limited motion, said by an orthopedic consultant to be the result of infection.

Laboratory Findings.—Roentgen-ray examination of the gallbladder gave no evidence of stone. Hypertrophic changes were found in the joints. The urine showed a small trace of albumin, and bile +. Red blood cells were seen twice in the sediment, but a culture was negative. No autolysis of blood clot. The stools showed a positive guaiac test twice, a negative test once; bile was present; microscopic examination showed excess of fatty acids and soaps.

Diagnosis (by Dr. Roger I. Lee).—Hanot's cirrhosis, apparently secondary to a localized infection in the biliary passages.

CASE 10 (15).—A. L., (E. M. 179,058) was a married Italian laborer, aged 51 years, who had drunk four or five glasses of whiskey and three or four glasses of beer a day for twenty years. The patient had been in the hospital five years before with a diagnosis of advanced cirrhosis of the liver and acute infection. He then had to be tapped three times in twenty-five days. During that period at the hospital he was operated on and an omentopexy was performed. Since then he had been tapped frequently but the ascitic fluid continued to recur with increasing rapidity. The liver at the time of operation was found to be small and hobnail in character.

TABLE 1.—BASAL METABOLISM DATA OF NORMAL CONTROLS

Subject's Number and Initials	Height	Weight	Age	Total Calories per Hour	Percentage Variation from Normal Standards	
					DuBois Surface Area Formula	Harris Benedict Tables
1. J. J. T.	160	57.0	24	65.5	+ 4	+ 5
2. B. A.	178	67.3	26	80.3	+11	+13
3. J. C. A.	176	60.4	27	74.2	+ 7	+12
	...	59.7	...	73.8	+ 7	+12
4. J. B. A.	170	64.8	23	74.3	+ 7	+ 8
5. F. R.	187	73.2	30	71.3	— 8	— 5
Average deviation					+ 5	+ 8

Physical examination showed a very poorly nourished and jaundiced Italian with slight dyspnea, whose teeth were in very poor condition. Heart measurements, 6 cm. to right of midsternal line, 15½ cm. to left in the fourth interspace. The sounds were of good quality. The abdomen measured 116½ cm., the chest 88½ cm. There were signs of much fluid in the abdomen and the veins were markedly dilated. In the legs also the veins were dilated.

Laboratory Findings.—Urinary examination was negative, except that bile was present. No autolysis of blood clot in twenty-four hours. The nonprotein nitrogen of the blood was 36 mg. per 100 c.c. The patient was tapped eleven times in seventy-five days and an average of 7 pints of fluid was obtained, which showed a specific gravity of about 1.015, about 40 cells per c. mm., most of which were lymphocytes. Thorough chemical studies of the ascitic fluid are reported by Denis and Minot in Table 2 of their paper. These studies show that the concentration of urea, uric acid, and cholesterol in the fluid could be influenced by changes in diet.

Impression.—A case of very severe alcoholic cirrhosis of long duration.

CASE 11 (16).—W. K. (Brigham Hospital, 22,290) was a laborer aged 65 years, who had acquired syphilis eleven years before entry. For the past two years he had had nocturia, from 2 to 4 times. All of his teeth had been extracted two years before, but he had never had false teeth. Two weeks

before entry be noticed that his abdomen was swollen. He had no pain and continued to work. He was easily tired, however, and had considerable coughing at night. Both legs seemed swollen at that time.

The patient showed considerable loss of weight, edema of the feet and ankles, and a marked ascites. Peripheral vessels showed marked arteriosclerosis.

The patient was tapped and 8 liters of ascitic fluid were obtained. The liver and spleen could not be felt.

Laboratory Findings.—Roentgen-ray examination of the lungs showed adenopathy in hilus regions, and mottling of both lungs.

After tapping, the fluid did not recur, and the patient was discharged relieved, with a diagnosis of alcoholic cirrhosis of the liver, arteriosclerosis, ascites and question of pulmonary and peritoneal tuberculosis.

Impression.—This case gave the impression of being a fairly severe cirrhosis with the first signs of liver insufficiency.

CASE 12 (17).—E. M. (E. M. and E. S. 210,942) was a married man, aged 54 years, with no occupation. He had drunk from one-half to one pint of gin and whiskey every day for twenty years, but for the past ten years he had drunk very little. A year before entry his abdomen had become large, but it diminished in size after rest and treatment. Three months before entry it again became swollen, and in the last two weeks had markedly increased in size. He had had edema of the legs for three months, and of the scrotum for four days, and had lost much weight. He had never been tapped.

Physical examination showed a very thin man. The sclerae were possibly slightly yellow. The arteries were sclerotic, and the brachials tortuous. The abdomen was full of fluid. The veins of the abdominal and chest walls were markedly dilated.

The patient was tapped and 16½ quarts of ascitic fluid were taken from the abdomen. The edge of the liver could not be felt after this. Six days later the abdomen was again filled as at entrance.

The patient was operated on by Dr. E. P. Richardson. About 3 gallons of yellow, serous fluid were evacuated. The liver was contracted and hobnail in type. The spleen was twice its normal size. The stomach appeared normal. Omentopexy was performed.

Laboratory Findings.—Examination of the blood showed a red cell count of 3,500,000; 80 per cent. hemoglobin; moderate achromia; 35 mg. nonprotein nitrogen per 100 c.c. blood. Autolysis of blood clot was negative once, but positive once in forty-eight hours. In the ascitic fluid there were 45 cells per c.mm. of which 60 per cent. were lymphocytes and 36 per cent. endothelial cells. The chemical analysis of the fluid is reported as Case 6 in Table 1 by Denis and Minot.

The patient died October 17. Necropsy (3646) showed: Chronic interstitial hepatitis; slight hypertrophy of spleen; ascites; slight icterus; chronic pleuritis; hemorrhagic edema of lungs; slight arteriosclerosis; operation wound, omentopexy.

CASE 13 (18).—S. B. (E. M. 210,639) was a married cobbler, aged 38 years, with moderate habits. Four weeks before entry, he had chills and fever for one day, with a cramplike constant pain which did not radiate, in the right hypochondrium. He had had no pain since then, but his legs had become swollen and the abdomen distended, and for two weeks he had been jaundiced.

Physical examination showed the patient to be slightly cyanotic. His abdomen was distended and there were signs of the presence of much fluid. There was marked edema of the legs and thighs. The heart was felt in the fourth interspace, 14 cm. to the left of the midsternal line. Its sounds were regular and normal, except for a slight blowing systolic murmur at the apex, which was transmitted slightly to the axilla.

Laboratory Findings.—Roentgen-ray examination showed the heart shadow to be within normal limits. Phenolsulphonephthalein test showed 30, 55, and 51 per cent. respectively to be excreted in two hours. Twenty-seven mg. nonprotein nitrogen per 100 c.c. were found in the blood. Two urinary examina-

tions showed the slightest possible trace of albumin. The blood pressure was 145 systolic.

Subsequent History.—The patient was discharged, but reentered the hospital two weeks afterward because of recurring edema of the legs and abdomen. Dr. D. L. Edsall in a note in the record stated that he thought the case was one of polyserositis, and that the liver trouble was more important than the cardiac condition. When the patient was tapped Oct. 26, 7000 c.c. fluid were obtained. This was turbid, and had a specific gravity of 1.011. It contained 350 cells per c.mm. of which 62 per cent. were small lymphocytes. A guinea-pig inoculated with the fluid developed tuberculosis of the spleen. The chemical analysis of the fluid is reported as Case 9, Table 1, in the paper by Denis and Minot.

October 30 the patient grew irrational, his intestines were dilated and there were signs of fluid in the pericardium. He died the same day. A necropsy was refused.

First Diagnosis.—Cardiac decompensation (slight), and question of cirrhosis of the liver.

TABLE 2.—BASAL METABOLISM DATA IN LIVER DISEASE

Patient's Number and Initials	Height	Weight	Age	Temp., F.	Total Calories per Hour	Percentage Variation from Normal Standards	
						DuBois Surface Area Formula	Harris Benedict Tables
8. H. H. H.	170.0	62.5	42	97.6	70.4	+ 6	+13
9. T. J. J.	167.2	58.2	51	98.2	66.1	+ 7	+17
10. E. H. DeC.	163.0	46.0	29	98.6	61.7	+ 7	+12
11. N. P.*	143.5	53.0	53	97.6	48.6	— 3	— 1
12. M. F.*	154.3	54.1	28	98.0	53.8	— 4	— 3
13. F. S.	175.0	58.6	45	99.4	65.5	± 0	+ 9
14. F. B. C.	180.5	73.3	27	97.0	81.2	+ 7	+ 8
15. A. L.	163.5	63.4	51	98.4	71.0	—11	— 4
	163.5	64.2	51	99.6	56.4	+11	+20
16. W. K.	169.0	51.9	65	97.3	55.5	+ 1	+12
17. E. M.	177.5	68.6	54	97.8	57.1	—18	—11
18. S. B.	164.0	84.4	38	....	75.2	± 0	+ 1
19. F. P.	170.0	56.8	22	97.2	74.5	+13	+15
Average deviation						+ 1	+ 7

* Females.

Diagnosis at Death.—Multiple serositis, ascites, left hydrothorax.

CASE 14 (19).—F. P. (W. M. 213,436) was an unmarried butcher, aged 22 years. Fifteen months before he was operated on for gangrenous appendix. Three months later two ribs, a portion of the abdominal wall, and a wedge of the liver were removed, because of actinomycosis. At the time of this study he had a typical case of acute catarrhal jaundice, of one month's duration, from which he was beginning to recover.

Diagnosis.—Acute catarrhal jaundice.

DISCUSSION

The Basal Metabolism.—Several publications by Grafe [33] showed that in animals with Eck fistula with the circulation of the liver cut off [1][33] or whose liver had been removed, [2][33] the total metabolism was

33. (1) Grafe, E. and Fischer, F.: Der Einfluss der Leberausschaltung auf den respiratorischen Stoffwechsel. Deutsch. Arch. f. klin. Med. **108**:516, 1912. Das Verhalten des Gesamtstoffwechsel bei Tieren mit Eck'scher Fistel **104**:28, 1911. (2) Grafe, E., and Deneke, G.: Ueber den Einflus der Leberextirpation auf Temperatur und respiratorischen Gaswechsel, Deutsch. Arch. f. klin. Med. **118**:249, 1915.

reduced as much as one third. With this drop in metabolism, however, there was a distinct fall in temperature which alone might cause a similar drop in heat production. The animals with the liver removed lived at most only fifteen hours. If the liver is essential to a normal basal metabolism, then very severe liver disease might show abnormal values.

In Tables 1 and 2 are summarized our data for basal metabolism. The usual procedure was followed in all these cases—the subjects had not eaten for fifteen or eighteen hours, and the tests were made only after complete muscular relaxation of more than half an hour's duration. The twelve cases of liver disease are described in the case histories. The patients all had distinct involvement of the liver, most of them with very advanced disease and severe symptoms. They were chosen largely because of their varied types of disorder. It was thought best to report the variations by both the DuBois [34] and the Harris-Benedict [35] standards, but the average by both methods is well within the normal limits. By the DuBois method, only two cases are really outside normal limits, and this may be explained by factors other than the liver. E. M. was very emaciated and had far advanced cirrhosis—a man who, because of his emaciation alone, should have had a reduced metabolism. F. P., a nervous, high-strung young man, should normally have had a slightly elevated metabolic rate. Therefore, it seems justifiable to conclude that the basal metabolic rate in liver disease is normal, and that either the liver is not an important regulator of the metabolic rate, or that, even in severe disease, it is adequate to accomplish this function.

Response to a Protein-Rich Meal.—The reactions of metabolism after the ingestion of large quantities of meat are best shown in Tables 3 and 4, and in the charts in which are graphically portrayed the height of metabolism and the duration of the experiment. It is readily seen that in all but three cases, the response to protein food is quite similar to that in the normal individual. The elevation of metabolism occurs as rapidly as in normal cases when there is portal obstruction with rapidly recurring ascites, and also with very severe liver disease, with practically complete bile duct obstruction. Tests in two cirrhosis cases and in one case of gallstones failed to show any specific rise of metabolism. As there was no marked rise in the urinary output of nitrogen, it may be assumed either that the protein was not being

34. (1) Gephart, F. C., and DuBois, E. F.: The Basal Metabolism of Normal Adults with Special Reference to Surface Area, Arch. Int. Med. **17**:902 (June) 1916. (2) Aub, J. C., and DuBois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:831 (June) 1917.

35. Harris, J. A., and Benedict, F. G.: Biometric Standards. Publication No. 279, Carnegie Inst. Washington.

TABLE 3.—Specific Dynamic Action in Normal Controls and Exophthalmic Goiter

Patient's Number and Initials	Condition	Grams of Meat Eaten	Respiratory Quotient					Total Metabolism					Percentage Increase Over Basal Metabolism			
			Basal	Hours after Meal				Basal	Hours after Meal				Hours after Meal			
				2	3	4	5		2	3	4	5	2	3	4	5
Normal Controls																
1. J. J. T.	Normal after operation	350	0.94	0.88	0.83	0.80	....	65.5	77.1	85.8	84.0	....	18	31	28	
2. B. A.	Normal	350	0.71	0.82	0.73	0.75	0.73	80.3	87.6	85.9	77.8	85.9	9	7	—3	7
3. J. C. A.	Normal	350	0.80	0.93	0.86	0.87	0.77	74.2	84.6	85.5	80.4	78.4	14	15	8	6
		500	0.80	0.88	0.83	0.82	0.85	73.8	89.4	90.4	86.7	89.5	21	22	18	21
4. J. B. A.	Normal	500	0.75	0.78	0.79	0.77	....	74.3	84.8	84.1	87.0	....	14	13	17	
5. F. R.	Normal	500	0.88	0.78	0.80	0.78	0.79	71.3	79.2	83.3	84.2	82.8	11	17	18	16
Average		...	0.81	0.85	0.81	0.80	0.79									
Exophthalmic Goiter																
6. E. T. B.	Basal rate +56%	470	0.74	0.72	0.77	0.80	0.77	96.1	110.8	105.9	114.5	111.6	15	10	19	16
7. W. H.	Basal rate +56%	500	0.80	....	0.91	0.82	0.80	90.7	.....	100.7	103.8	106.8	..	11	14	18
Average		...	0.77	....	0.84	0.81	0.78									

TABLE 4.—Specific Dynamic Action in Liver Disease

Patient's Number and Initials	Diagnosis	Grams of Meat Eaten	Respiratory Quotient					Total Metabolism					Percentage Increase Over Basal Metabolism			
			Basal	Hours after Meal				Basal	Hours after Meal				Hours after Meal			
				2	3	4	5		2	3	4	5	2	3	4	5
8. H. H. H.	Carcinoma	170	0.78	0.79	0.76	0.77	....	70.4	73.3	74.9	74.6	....	4	6	6	
9. T. J. J.	Carcinoma, obstr. jaun.	500	0.77	0.84	0.81	0.77	0.80	66.1	77.6	79.7	81.7	83.5	17	21	23	26
10. E. H. DeC.	Sarcoma, obstr. jaun.	500	0.77	0.79	0.88	0.80	0.88	61.7	68.9	76.3	76.6	81.8	12	24	24	33
11. N. P. ♀	Gall stones	349	0.90	0.90	0.87	0.87	0.81	48.6	51.2	49.2	50.5	50.0	5			
12. M. F. ♀	Portal obstr., cirrhosis	500	0.75	0.87	0.82	0.80	0.80	53.8	62.4	64.6	64.7	65.9	16	20	20	22
13. F. S.	Early cirrhosis	350	0.84	0.80	0.79	0.71	0.75	65.5	74.7	78.5	82.8	80.9	14	20	26	23
14. F. B. C.	Hanot's cirrhosis	500	0.83	0.93	0.83	0.83	0.77	81.2	97.3	97.3	96.8	98.8	20	20	19	22
15. A. L.	Cirrhosis	363	0.76	0.75	0.73	0.74	0.80	71.0	70.8	71.5	72.5	73.3	..	..	2	3
		440	0.89	....	....	0.76	0.78	56.4	....	....	70.3	68.0	..	..	25	21
16. W. K.	Cirrhosis	418	0.87	0.84	0.85	0.80	0.81	55.5	63.2	66.0	67.1	70.4	14	19	21	27
17. E. M.	Cirrhosis	375	0.74	....	0.71	0.71	0.67	57.1	....	60.6	56.7	61.2	..	6	0	7
Average		...	0.81	0.83	0.81	0.78	0.78									

absorbed, or that possibly, which is unlikely, it was being deposited. One of these patients (A. L.) later showed a quite normal response, and so it is very likely that these three cases were due to faulty absorption resulting from the venous congestion of cirrhosis. It is difficult to explain any lack of absorption of protein as being due to gallstones. It is of interest that A. L., who showed no markedly increased nitrogen excretion or specific dynamic action after his first test meal, did show a distinct increase in the protein content of the ascitic fluid after the meal. This suggests that part of the protein escaped into the peritoneal cavity to be reabsorbed, as Müller and Schultz believe.[23] In order to catch a

TABLE 5.—CALORIE INCREASE PER HOUR AFTER MEAT TEST

Patient's Number and Initials	Protein Calories			Total Calories Average			Ratio of Total Increase to Protein Increase
	Basal	Maximal	Increase	Basal	Maximal	Increase	
Controls							
1. J. J. T.	15.48	17.05	1.57	65.47	84.90	19.43	12.31
2. B. A.	12.09	34.15	22.06	80.32	83.99	3.67	0.17
3. J. C. A.	14.82	35.68	20.86	73.84	89.02	15.18	0.73
	10.07	26.72	16.65	74.17	84.45	10.28	0.62
4. J. B. A.	10.26	22.37	12.11	74.33	89.99	10.66	0.88
5. F. R.	16.06	30.83	14.77	71.31	83.44	12.13	0.82
Exophthalmic Goiter							
6. E. T. B.	10.66	42.09	31.43	96.09	110.45	14.36	0.46
7. W. H.	13.57	40.24	26.67	90.68	105.09	14.41	0.54
Liver Disease							
8. H. H. H.	6.95	16.62	9.67	70.41	74.72	4.31	0.45
9. T. J. J.	6.63	33.14	26.51	66.10	81.09	14.99	0.57
10. E. H. DeC.	8.51	32.61	24.10	61.73	78.51	16.78	0.70
11. N. P. *	3.82	19.59	15.77	48.45	53.77	5 32	0.34
12. M. F. *	6.50	13.02	6.52	53.84	65.16	11.32	1.73
13. F. S.	7.62	22.77	15.15	65.49	83.48	17.99	1.19
14. F. B. C.	12.25	25.61	13.36	81.45	97.55	16.10	1.20
15. A. L.	6.15	12.72	5.57	71.06	71.96	0.90	0.16
	9.83	16.73	6.90	56.42	71.72	15.30	2.21
16. W. K.	16.35	24.26	7.91	55.51	69.50	13.99	1.76
17. E. M.	5.14	10.23	5.09	57.12	58.91	1.79	0.35

* Females.

possibly delayed response this test was repeated, and four and one-half hours after the test meal a definite specific dynamic action was found. In this case, therefore, a delayed response is suggested. In all the jaundiced cases, the dynamic action is quite normal. This agrees with the findings of Glaessner.[15]

It is very difficult to find a satisfactory way of comparing the intensities of the dynamic action. The most logical method seems to be the ratio: $\frac{\text{Total calories increase}}{\text{Protein calories increase}}$, for this should show the total response for each extra calorie of protein metabolism. This ratio gives similar response in all cases (Table 5), except in one normal control, J. J. T., where the response is far too great for the protein increase. In the remaining tests, the highest ratios are in the cases of cirrhosis. The two cirrhosis tests with low ratios showed practically no response to

the protein meal and therefore can hardly be counted in this regard. The other five tests suggest that in cirrhosis the dynamic action is high.

The partition of foodstuffs utilized is not very clear-cut, and varies markedly in the different experiments. On the whole, however, the grams of carbohydrate utilized are increased at the expense of fat during the specific dynamic action. The increase in protein calories is in general greater than the increase in total calories (Table 5). Our results are calculated to give protein the greatest possible proportions in the metabolism, and in spite of this, it must be concluded that, though the protein increase is enough to account for all the rise of metabolism, it is aided by an increase of carbohydrate, and a diminution in the burning of fat. This agrees with the findings of Aub and DuBois [4] but disagrees somewhat with Gigon,[27] who thought that all the extra calories came from protein.

The two cases of exophthalmic goiter which we have studied have given results which agree with the findings of DuBois.[5] In spite of their high basal rate, the response to a large quantity of meat was an increase of metabolism as rapid and intense as in the normal individual.

CONCLUSIONS

1. The basal metabolism in twelve cases of liver disease was essentially within normal limits. The liver is, therefore, either not an important regulator of the metabolic rate, or it is adequate for this purpose even when severely diseased.

2. The rate of absorption and utilization of protein in large quantities was usually normal, even in severe cirrhosis. In two cases of cirrhosis and one of gall stones, the utilization of the protein was delayed or absent. Marked portal obstruction caused no delay in the appearance of the specific dynamic action of protein.

3. The cases of cirrhosis showed, on the whole, the highest metabolic response to protein catabolism.

4. The conclusion seems justified that either the liver is not the main site of the specific dynamic action of protein, or that it can adequately perform that function even in disease.

5. The specific dynamic action of protein results from an increased combustion of protein and carbohydrate, rather than of fat.

6. The observation of DuBois that in exophthalmic goiter a normal increase in heat production, due to protein, is superimposed on the high basal rate is confirmed.