

## METABOLISM STUDY OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH SPLENOMEGALY \*

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### I. INTRODUCTION

The interesting syndrome of chronic acholuric, pleiochromic jaundice without the usual syndrome of biliary intoxication associated with anemia and splenomegaly was first noted clinically by Murchison<sup>1</sup> in 1883. Minkowski<sup>2</sup> in 1900, however, reported a very complete study of a group of cases occurring in one family. Excellent reviews of the subject, together with the literature, have been presented by Tileston and Griffin<sup>3</sup> and by Thayer and Morris,<sup>4</sup> so we shall in this paper consider only those details which have relation to the experimental work to be described.

Besides the usual hereditary form of this disease, there is a familial type and a congenital type, in which the disease dates from birth and appears in only one of the family. It may be noted from the history that the case described in this paper belongs to this type. Another type is the so-called "acquired" form, in which the disease usually appears in childhood or adolescence.<sup>5</sup>

The interesting work of Whipple and Hooper<sup>6</sup> has placed the possibility of a purely hemolytic jaundice on a firm scientific foundation. They think it possible that the endothelium of the blood-vessels is the agent which brings about the rapid change of hemoglobin to bile-pigment, and that this mechanism comes into play when there has been a destruction of many red cells with much hemoglobin free in the plasma.

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\* From the Laboratory of Dr. James P. McKelvy, Pittsburgh.

1. Murchison: *Diseases of the Liver*, Ed. 3, 1885, 481.

2. Minkowski: *Verhandl. d. Cong. f. inn. Med.*, 1900, xviii, 316; *Deutsch. Klin.*, 1905, v, 651.

3. Tileston and Griffin: *Am. Jour. Med. Sc.*, 1910, cxxxix, 847.

4. Thayer and Morris: *Bull. Johns Hopkins Hosp.*, 1911, xxii, 85.

5. Richards and Johnson: (*Jour. Am. Med. Assn.*, 1913, lxi, 1586), have reported an interesting and well-studied case of congenital hemolytic jaundice. See also Pel; *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 239; Quadri; *Virchows Arch. f. path. Anat.*, 1914, ccxv, 151, and McNee, *Jour. Path. and Bacteriol.*, 1914, xviii, 325.

6. Whipple and Hooper: *Jour. Exper. Med.*, 1913, xvii, 612.

Many theories have been put forth to explain this peculiar syndrome. Pick<sup>7</sup> thought that there was present a congenital communication between the bile passages and the lymphatics. Hayem's<sup>8</sup> latest view is that it is due to syphilis. Minkowski believes that it is due to a congenital perverted function of the liver cells, and on this account, the bile is excreted into the lymphatics instead of into the bile capillaries. Chauffard's<sup>9</sup> discovery that in this syndrome there is present an increased fragility of the red cells opened up a new path for theories. The disease could be explained on this basis: that owing to the increased susceptibility of the red cells to hemolytic agents, the anemia develops and regeneration types of red cells appear in the circulation.

This increased destruction of red cells then leads to an increased formation of bile pigment and the resulting icterus. As several have failed to find hemolysins in the blood, it may be said that the increased destruction of the red cells takes place in the spleen, which leads to an increased work of the spleen and therefore accounts for the splenomegaly. This hemolytic theory is the one generally accepted to account for the symptom-complex. Troisier thinks that the fragility of the red cells depends on the fact that they have already become sensitized by union with a hemolytic amboceptor. Hutchison and Panton,<sup>10</sup> in a study of a case of the "congenital" type, think that the production of the defective red cells is a factor of considerable importance in the ultimate cause of this condition. Hawkins and Dudgeon<sup>11</sup> are also of the opinion that the primary change lies in the blood-forming organs and not in the biliary system. Widal<sup>12</sup> and his school think that the red cells are destroyed in the blood and the bile pigment is formed there. The splenomegaly then results from the increased work due to bile destruction. Banti thinks the primary lesion is in the spleen. The view of Vaquez and Aubertin has found most favor. They believe the jaundice is due to the bilirubin circulating in the blood, which is pro-

7. Pick: *Wien. klin. Wchnschr.*, 1903, xvi, 493.

8. Hayem: *Presse méd.*, 1898, vi, 121; *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1908, Series 3, xxv, 122.

9. Chauffard: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1901, Series 3, xviii, 444; *Semaine méd.*, 1907, xxvii, 25; *Presse méd.*, 1907, xv, 345; *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1907, Series 3, xxiv, 1169 and 1367; *Compt. rend. Soc. de biol.*, 1907, lxxiii, 672; *Semaine méd.* 1908, xxviii, 49; *Allg. Wien. med. Ztg.*, 1908, liii, 462; *Bull. et mém. Soc. méd. d. Hôp. de Paris*, 1908, Series 3, xxv, 411; 1908, Series 3, xxvi, 94; 1909, xxvii, 293.

10. Hutchison and Panton: *Quart. Jour. Med.*, 1909, ii, 433.

11. Hawkins and Dudgeon: *Quart. Jour. Med.*, 1909, ii, 165.

12. Widal: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1902, Series 3, xix, 984; 1907, Series 3, xxiv, 1127, 1354; 1909, Series 3, xxviii, 73; 1908, Series 3, xxv, 486; *Gaz. d. hôp.*, 1907, lxxx, 1275; *Presse méd.*, 1907, xv, 641; *Compt. rend. Soc. de biol.*, 1907, lxxiii, 346; 1908, lxiv, 496 and 655; 1909, lxvi, 927 and 950; *Tribune méd.*, 1907, xxxix, 711; *Arch. d. mal. du coeur*, 1908, 1, 193.

duced by the liver cells as a result of attempts to change the increased amount of pigment arising from the destruction of the corpuscles. Whipple and Hooper<sup>6</sup> claim, however, that hemoglobin can be converted into bile pigments without participation of the liver. Roth<sup>13</sup> believes that hemolytic jaundice is a 'primary disease of the blood. Chauffard<sup>14</sup> thinks he has evidence pointing conclusively to an inherited taint, syphilis or tuberculosis, on which is added some abnormal action on the part of the spleen, as the factors responsible for congenital hemolytic jaundice.

It was thought that a complete metabolic study of this symptom-complex might throw some light on this disease. This was especially desirable on account of the fact that very little work has been done in this condition, from the metabolic standpoint. Tileston and Griffen studied the total nitrogen, urea-nitrogen, ammonia-nitrogen, creatin and creatinin in a case of chronic family jaundice for a period of three days. On a creatin- and purin-free diet, they found that the creatinin and urea values were normal, those for ammonia somewhat high. They found about 0.06 gm. of creatin in the urine per day and think the endogenous uric acid is distinctly increased. They report only one estimation of the uric acid in the complete study, however, so this result cannot be considered conclusive. They found, also, that tests for alimentary glycosuria and levulosuria were negative or inconclusive.

Minkowski<sup>15</sup> mentions that in a case of family hemolytic jaundice, Haal found an increased excretion of uric acid and a decided increase in the amount of iron in the urine.

Certain metabolic studies have been carried out in Banti's disease. It will be recalled that the name "Banti's disease" is reserved for those cases in which liver enlargement is secondary to the progressive enlargement of the spleen and associated with recurrent attacks of anemia and repeated hemorrhages from the stomach and bowels. As this disease is somewhat similar to the case described in this paper, it will be of value to review the metabolism studies carried out in Banti's disease. Umber<sup>16</sup> found a toxogenic decomposition of protein in a case of Banti's disease. He did not think it was due to the anemia present, but since the protein destruction disappeared after the removal of the spleen, he thought this destruction of the protein was due to a toxic agent produced in the spleen. This substance not only produced the anemia, but also affected the general metabolism of the organism.

In another case, with similar clinical symptoms, Umber found a retention of nitrogen and periodic variations in the excretion of the

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13. Roth: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 137.

14. Chauffard: *Ann. d. méd.*, 1914, l, 1.

15. Minkowski: *Diseases of Digestive System*, edited by Billings, p. 349.

16. Cited by Umber: *Lehrbuch der Ernährung*, Berlin, 1909, p. 17.

urinary purin nitrogen. These values only slightly exceeded the upper limits for the normal excretion. The highest purin nitrogen excretion was 0.258 gm. Halpern,<sup>17</sup> in a case of splenic anemia, found that the average purin nitrogen excretion, on a purin-free diet, for a period of three days, was 0.253 gm.

## II. CLINICAL DATA

*Patient.*—M. E. H., a girl aged 11, born in U. S. A., was first seen Nov. 26, 1913.

*Family History.*—Father, mother, one brother and two sisters are all living and well. No other member of the family is afflicted in the same manner as the patient. There is no history of consanguinity, alcoholism, lues, tuberculosis or cancer.

*Previous History.*—The patient had rubella, parotitis, varicella and pertussis. No history of scarlet fever or diphtheria. Tonsillitis several years ago. No pleurisy or pneumonia. Slight attack of bronchitis this winter. Six years ago had an acute illness, with temperature 106 for a few hours. On the second day the symptoms disappeared and in one week the patient was well. At this time the enlargement of the spleen was first noted. Patient has never been strong; was treated six years ago with x-rays for a period of two weeks.

*Present Illness.*—Child has always had waxen color with a lemon tint. There has been no pruritus, no epistaxis, no dyspnea and no gastric symptoms. Bowels are regular, no diarrhea. Stools have been normal in color, but for two years after birth they were very green. The appetite is variable. No nausea or vomiting. Since her illness, six years ago, the spleen has been growing larger and the size is variable. The jaundice has been present since three or four weeks after birth.

*Chief Complaint.*—Enlargement of the spleen and persistent jaundice.

*Examination.*—General: The patient is underdeveloped and poorly nourished, weighing 63½ pounds. The skin is of a lemon yellow color, and the mucous membranes are pale. There are no eruptions. The cervical glands of the left side are slightly enlarged; submaxillary glands are enlarged; the axillary and epitrochlears are not palpable. Temperature 98, pulse 112.

Head: The nose, mouth and pharynx are normal. Tonsils large and ragged. The cranial nerves are normal, the teeth good, the thyroid not enlarged.

Eyes: The conjunctivae have a lemon yellow color. The pupils react moderately slowly to light and accommodation. Nystagmus to the left.

Chest: No deformities, no enlargement of thymus.

Lungs: Clear throughout.

Heart: Overacting. A blowing systolic murmur at the apex, over the pulmonary area, and transmitted to the left. The pulmonic second sound is accentuated.

Abdomen: Moderately distended and tympanitic. No abnormal masses, no areas of tenderness nor rigidity.

Liver: Extends from fifth space. The edge is palpable one-half inch below the costal border in the mammary line. The edge is firm and normal in outline.

Spleen: Extends forward to within one-half inch of midline and downward to the lower border of the umbilicus.

Kidneys: Not palpable.

Appendix and Colon: Negative.

Extremities: No edema or tenderness over large bones. The knee-jerks are normal.

17. Von Noorden: Metabolism and Practical Medicine, ii, 368.

Urine: Deep amber, clear, acid, specific gravity 1.021, no protein, no sugar, no bile, indican very slight. Microscopically contains a few squamous epithelial cells and a few leukocytes and erythrocytes.

Blood-Count: December 6, red blood-cells, 3,560,000; hemoglobin, 48 per cent. (Sahli N. S.); white blood-cells, 11,200; polynuclears, 78 per cent.; small lymphocytes, 14 per cent.; large lymphocytes, 3 per cent.; transitionals, 0.5 per cent.; eosinophils, 4.0 per cent.; neutrophils, 0.5 per cent. The red corpuscles show a definite variation in size, poikilocytosis present in mild degree. The red corpuscles stain uniformly well. No abnormal granulations present. One nucleated red corpuscle seen in making differential count of 200 cells. Blood platelets are present but relatively scarce. Blood-count: Feb. 14, 1914, hemoglobin, 55 Sahli (N. S.), red blood-cells, 3,740,000; white blood-cells, 12,600; polynuclears, 65 per cent.; small lymphocytes, 24 per cent.; large lymphocytes, 6 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent. Poikilocytosis, anisocytosis, variation in staining. Moderate number megalocytes, many microcytes, no nucleated reds.

Stools: Negative for blood, parasites or ova.

Wassermann reaction is negative.

### III. HEMOLYSIS TESTS OF PATIENT'S BLOOD

The work of Vaquez and Ribierre has demonstrated that in conditions of obstructive jaundice, the erythrocytes have an increased resistance to hemolysis by hypotonic salt solution. Chauffard and others,<sup>18</sup> in contrast to these results, found that the corpuscles in three cases of chronic acholuric icterus presented a greatly diminished resistance. Chauffard found that in normal individuals hemolysis started on addition of 0.44 per cent. sodium chlorid solution and was complete at 0.36 per cent.

TABLE 1.—HEMOLYSIS TESTS OF PATIENT'S BLOOD, DEC. 14, 1913\*

|                 | Strength of NaCl Solution in Per Cent. |       |       |      |      |       |      |       |     |       |      |     |
|-----------------|--|-------|-------|------|------|-------|------|-------|-----|-------|------|-----|
|                 | 0.375                                  | 0.4   | 0.425 | 0.45 | 0.5  | 0.525 | 0.55 | 0.575 | 0.6 | 0.625 | 0.65 | 0.9 |
| Patient's blood | +++++                                  | +++++ | +++++ | ++++ | ++++ | ++++  | +++  | +++   | +++ | +++   | ++   | +   |
| Control normal  | +                                      | ++    | 0     | 0    | 0    | 0     | 0    | 0     | 0   | 0     | 0    | 0   |

\* Washed cells used. In this table +++++ equals complete hemolysis; ++++ equals moderate hemolysis; +++ equals slight hemolysis; ++ equals very slight hemolysis; + equals trace of hemolysis; 0 equals no trace of hemolysis.

In testing the osmotic resistance of the red cells of this patient, the same technic was used as that described by Richards and Johnson.<sup>5</sup> Table 1 contains the results obtained in this study, showing that the red cells of this patient had a lessened resistance toward salt solution.

18. Chauffard: *Compt. rend. Soc. de biol.*, 1902, liv, 1074. Von Stejskal: *Wien. klin. Wchnschr.*, 1909, xxii, 1701. Butler: *Quart. Jour. Med.*, 1913, vi, 145. Massaglia and Tarabina: *Gazz. d. osp. e. de clin.*, 1908, xxix, 778. Pel: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 239. Maliwa: *Deutsch. med. Wchnschr.*, 1913, xxxix, 154. Roth: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 137. Cade: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1908, xxv, 421.

## IV. METABOLIC DATA

The patient was placed on Folin's<sup>19</sup> diet in quantities of about one-half the original amounts. It consisted of:

Whole milk, 300 c.c.; cream, 150 c.c.; malted milk, 100 gm.; sugar, 10 gm.; salt, 4 gm.; butter, 5 gm.; eggs (minus shell), about 240 gm.; water, 1,000 c.c.

This diet contains approximately 60 gm. of protein, 75 gm. of fat and 112 gm. of carbohydrate, yielding 1,395 calories or about 50 calories per kilogram body weight of the patient.

Two ounces of the above-described diet was taken out daily and the following constituents estimated: total nitrogen, phosphorus, sulphur, iron, calcium and magnesium. The fat was estimated in the five-day sample, preserving 5 c.c. of each day's mixture by means of two drops of liquor formaldehydi.

TABLE 2.—THE NITROGEN METABOLISM—

| Date<br>1913 | Vol. | Acidity in Amt.<br>of N/10 NaOH<br>necessary to<br>neutralize<br>total urine | Total<br>Nitrogen<br>gm. | Urea Nitrogen |                  | Ammonia<br>Nitrogen |                  | Creatinin † |               |                  |
|--------------|------|--|--------------------------|---------------|------------------|---------------------|------------------|-------------|---------------|------------------|
|              |      |  |                          | gm.           | % of<br>total N. | gm.                 | % of<br>total N. | gm.         | Nitro-<br>gen | % of<br>total N. |
| 12/10        | 950  | 186.2  | 7.02                     | 6.01          | 85.6             | 0.32                | 4.5              | 0.48        | 0.174         | 2.50             |
| 12/11        | 1100 | 294.8  | 8.32                     | 7.06          | 84.8             | 0.34                | 4.0              | 0.45        | 0.163         | 1.96             |
| 12/12        | 975  | 327.6  | 8.35                     | 7.04          | 84.3             | 0.35                | 4.1              | 0.36        | 0.131         | 1.57             |
| 12/13        | 1175 | 305.5  | 8.36                     | 7.12          | 85.2             | 0.38                | 4.5              | 0.44        | 0.160         | 1.91             |
| 12/14        | 880  | 306.2  | 8.40                     | 7.20          | 85.7             | 0.36                | 4.3              | 0.44        | 0.160         | 1.90             |
| 12/15        | 1050 | 302.4  | 8.10                     | 7.18          | 88.6             | 0.32                | 4.0              | 0.42        | 0.152         | 1.88             |

\* Creatin was not present in the urine at any time.

*A. The Method Used in Urine Analysis.*—The nitrogen was estimated according to Kjeldahl, the total sulphur by Benedict's<sup>20</sup> method, total and ethereal sulphates by Folin's<sup>21</sup> method, the inorganic sulphates computed by subtracting the ethereal sulphates from the total sulphates and the neutral sulphur by subtracting the total sulphate sulphur from the total sulphur. The urea was estimated by Benedict's<sup>22</sup> method. The ammonia by Folin's method,<sup>23</sup> the total phosphorus by the Neumann method,<sup>24</sup> weighing the phosphorus as magnesium pyrophosphate. The iron was estimated by Neumann's<sup>25</sup> method, the total phosphates and earthy phosphates by titration with uranium acetate

19. Folin, O.: *Am. Jour. Physiol.*, 1905, xiii, 45.

20. Benedict: *Jour. Biol. Chem.*, 1909, vi, 363.

21. Folin: *Am. Jour. Physiol.*, 1905, xiii, li; *Jour. Biol. Chem.*, 1906, i, 131.

22. Benedict: *Jour. Biol. Chem.*, 1911, viii, 405.

23. Folin: *Ztschr. f. physiol. Chem.*, 1902, xxxvii, 161; *Am. Jour. Phys.*, 1903, viii, 330.

24. Neumann: *Ztschr. f. physiol. Chem.*, 1902-03, xxxvii, 129; 1904-05, xliii, 35.

25. Neumann: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 114.

solution; creatinin and creatin by Folin's methods<sup>19</sup>; uric acid by Folin's<sup>26</sup> method; calcium and magnesium by McCrudden's<sup>27</sup> method; amino-acid by Benedict and Murlin's method,<sup>28</sup> and total acidity by Folin's method.<sup>29</sup>

*B. Methods Used in the Analysis of the Food.*—The nitrogen by Kjeldahl method; total sulphur by Wolff and Osterberg's<sup>30</sup> modification of Benedict's method; calcium and magnesium by McCrudden's method, after ashing and extracting the ash with hydrochloric acid; the phosphorus and iron by Neumann's method. The fat was estimated in a five-day period by Soxhlet extraction.

*C. Methods Used in Analysis of Feces.*—The feces were marked off by means of carmin into a period of five days. The nitrogen was estimated by Kjeldahl method; sulphur by oxidizing with fuming acid,

#### —AND URINARY NITROGEN PARTITION \*

| Uric Acid |               |                  | Amino-Acid Nitrogen |                  | Undetermined Nitrogen |                  | Feces Total Nitrogen |                  | Nitrogen      |               |                |
|-----------|---------------|------------------|---------------------|------------------|-----------------------|------------------|----------------------|------------------|---------------|---------------|----------------|
| gm.       | Nitro-<br>gen | % of<br>total N. | gm.                 | % of<br>total N. | gm.                   | % of<br>total N. | gm.                  | % of<br>total N. | Intake<br>gm. | Output<br>gm. | Balance<br>gm. |
| 0.43      | 0.143         | 2.04             | 0.08                | 1.2              | 0.29                  | 4.1              | 0.77                 | 10.9             | 8.04          | 7.79          | + 0.25         |
| 0.35      | 0.120         | 1.44             | 0.18                | 2.2              | 0.46                  | 5.5              | 0.77                 | 9.3              | 8.15          | 9.09          | — 0.94         |
| 0.41      | 0.137         | 1.64             | 0.15                | 1.8              | 0.54                  | 6.5              | 0.77                 | 9.2              | 8.25          | 9.12          | — 0.87         |
| 0.33      | 0.110         | 1.32             | 0.20                | 2.4              | 0.39                  | 4.7              | 0.77                 | 9.2              | 8.05          | 9.13          | — 1.08         |
| 0.49      | 0.143         | 1.70             | 0.17                | 2.0              | 0.37                  | 4.4              | 0.77                 | 9.2              | 8.25          | 9.17          | — 0.92         |
| 0.41      | 0.137         | 1.70             | 0.14                | 1.7              | 0.17                  | 2.1              | 0.77                 | 9.5              | 8.37          | 8.87          | — 0.50         |

† Average creatinin coefficient equals 5.9 mg. of creatinin-nitrogen per kilogram of body weight.

followed by Benedict's method; phosphorus and iron by the Neumann method; calcium and magnesium by the same method as used for the food; the fat by Soxhlet extraction. Tables 2, 3 and 4 contain the results obtained in this study.

*Discussion of Table 2.*—In the period of five days, there was a loss of 4.06 gm. of nitrogen, which might be considered as evidence pointing toward a toxogenic destruction of protein in this patient. The absorption of nitrogen is normal. The urinary nitrogen partition is normal with the exception of the uric acid, which shows a decided increase. This increase might be due to the fact that owing to the hemolysis of the erythrocytes, nucleoprotein is liberated from which the uric acid is formed and thereby an increased urinary excretion of endogenous uric acid is produced. This result speaks in favor of an increased destruction of the red cells as being a part of the condition.

26. Folin: Ztschr. f. physiol. Chem., 1901, xxxii, 552.

27. McCrudden: Jour. Biol. Chem., 1911, x, 187.

28. Benedick and Murlin: Jour. Biol. Chem., 1913, xvi, 385.

29. Folin: Am. Jour. Physiol., 1903, viii, 265.

30. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

TABLE 3.—THE SULPHUR METABOLISM AND URINARY SULPHUR PARTITION

| Date 1913 | Vol. c.c. | Total S. gm. | Total sulphate S. |               | Ethereal sulphate S. |               | Inorganic sulphate sulphur |               | Neutral sulphur |               | Feces S. gm. | Sulphur    |            |             |
|-----------|-----------|--------------|-------------------|---------------|----------------------|---------------|----------------------------|---------------|-----------------|---------------|--------------|------------|------------|-------------|
|           |           |              | gm.               | % of total S. | gm.                  | % of total S. | gm.                        | % of total S. | gm.             | % of total S. |              | Intake gm. | Output gm. | Balance gm. |
| 12/10     | 950       | 0.68         | 0.58              | 85.3          | 0.18                 | 26.5          | 0.40                       | 58.8          | 0.10            | 14.7          | 0.156        | 0.50       | 0.836      | — 0.336     |
| 12/11     | 1100      | 0.79         | 0.70              | 88.6          | 0.07                 | 8.8           | 0.63                       | 79.8          | 0.09            | 11.4          | 0.156        | 0.41       | 0.790      | — 0.38      |
| 12/12     | 975       | 0.74         | 0.64              | 86.5          | 0.14                 | 18.9          | 0.50                       | 67.6          | 0.10            | 13.5          | 0.156        | 0.54       | 0.896      | — 0.356     |
| 12/13     | 1175      | 0.73         | 0.61              | 83.5          | 0.13                 | 17.8          | 0.48                       | 65.7          | 0.12            | 16.4          | 0.156        | 0.46       | 0.886      | — 0.426     |
| 12/14     | 880       | 0.75         | 0.65              | 86.6          | 0.35                 | 46.7          | 0.30                       | 39.9          | 0.10            | 13.3          | 0.156        | 0.52       | 0.906      | — 0.386     |

*Discussion of Table 3.*—The urinary sulphur partition is normal in character, with the exception of a marked increase in the excretion of the ethereal sulphates on the first and last days of the metabolism experiment. This is due, no doubt, to an increased intestinal putrefac-

TABLE 4.—THE MINERAL METABOLISM—

| Date  | Urine   |         |         |                    |               |                     |               |              | Feces   |         |
|-------|---------|---------|---------|--------------------|---------------|---------------------|---------------|--------------|---------|---------|
|       | CaO gm. | MgO gm. | Fe gm.  | Total phosphate P. |               | Earthy phosphate P. |               | Total P. gm. | CaO gm. | MgO gm. |
|       |         |         |         | gm.                | % of total P. | gm.                 | % of total P. |              |         |         |
| 12/10 | 0.304   | 0.292   | 0.00877 | 0.62               | 91.2          | 0.17                | 24.7          | 0.63         | 0.76    | 0.26    |
| 12/11 | 0.426   | 0.264   | 0.00872 | 0.75               | 96.1          | 0.20                | 25.6          | 0.78         | 0.76    | 0.26    |
| 12/13 | 0.434   | 0.266   | 0.00874 | 0.66               | 94.3          | 0.12                | 17.1          | 0.70         | 0.76    | 0.26    |
| 12/14 | 0.640   | 0.254   | 0.00871 | 0.66               | 88.0          | 0.34                | 45.3          | 0.75         | 0.76    | 0.26    |
| 12/15 | 0.258   | 0.208   | 0.00881 | 0.60               | 92.3          | 0.24                | 36.9          | 0.65         | 0.76    | 0.26    |

tion. In the five days the patient lost 1.88 gm. of sulphur. This would be expected on account of the fact that our patient was also losing nitrogen.

*Discussion of Table 4.*—In the five-day metabolism experiment the patient lost 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., and the amounts of total phosphates and earthy phosphates may be considered normal. There was also an iron loss of 0.1199 gm. The metabolism of iron in the case studied is of special interest on account of the relation of the spleen to the disintegration of red cells, and also on account of the increased hemolysis present in this disease.<sup>31</sup>

To interpret our results, it will be necessary to review briefly some of the more important papers that have appeared on the metabolism of iron. Lehmann, Müller, Munk, Senator and Zuntz<sup>32</sup> in 1893 published an extended study of the metabolism of the professional fasters,

31. For discussion of iron in food and its function in nutrition see Sherman: Bulletin 185, U. S. Dept. Agric., Off. Exper. Sta., 1907.

32. Lehmann, Müller, Munk, Senator and Zuntz: Arch. Path. Anat. u. Phys. (Virchow), 1893, p. 131, Supp.



Cetti and Breithaupt. During a ten-day fast, Cetti lost 7.3 mg. iron in the feces per day. Breithaupt fasted six days and lost 7.7 mg. iron in the feces per day. Stockman and Grieg<sup>33</sup> studied three normal cases and one chlorotic as regards the iron metabolism. Their results may be seen in Table 5.

TABLE 5.—IRON METABOLISM IN CASES OF STOCKMAN AND GRIEG

| Experi-<br>ment<br>No. | Subject | Age | Iron in<br>Food<br>mg. | Iron in<br>Feces<br>mg. | Iron in<br>Urine<br>mg. | Bal-<br>ance<br>mg. |
|------------------------|---------|-----|------------------------|-------------------------|-------------------------|---------------------|
| 1                      | man     | 20  | 6.2                    | 5.07                    | 1.27                    | — 0.14              |
| 2                      | man     | 35  | 6.2                    | 8.10                    | 1.23                    | — 3.13              |
| 3                      | man     | 20  | 5.6                    | 10.87                   | 0.67                    | — 5.94              |

## —(CALCIUM, MAGNESIUM, PHOSPHORUS AND IRON)

| Feces                  |             | Balance         |                |                   |                |               |                |               |                |
|------------------------|-------------|-----------------|----------------|-------------------|----------------|---------------|----------------|---------------|----------------|
| Phos-<br>phorus<br>gm. | Iron<br>gm. | Calcium<br>oxid |                | Magnesium<br>oxid |                | Phosphorus    |                | Iron          |                |
|                        |             | Intake<br>gm.   | Balance<br>gm. | Intake<br>gm.     | Balance<br>gm. | Intake<br>gm. | Balance<br>gm. | Intake<br>gm. | Balance<br>gm. |
| 0.48                   | 0.02396     | 0.93            | — 0.134        | 0.32              | — 0.292        | 1.2           | + 0.04         | 0.0084        | — 0.0234       |
| 0.48                   | 0.02396     | 0.93            | — 0.256        | 0.38              | — 0.144        | 1.3           | + 0.04         | 0.0096        | — 0.0231       |
| 0.48                   | 0.02396     | 1.04            | — 0.154        | 0.36              | — 0.166        | 1.15          | — 0.03         | 0.0088        | — 0.0239       |
| 0.48                   | 0.02396     | 1.20            | — 0.20         | 0.34              | — 0.174        | 1.17          | — 0.06         | 0.0084        | — 0.0244       |
| 0.48                   | 0.02396     | 1.28            | + 0.262        | 0.32              | — 0.148        | 1.21          | + 0.08         | 0.0086        | — 0.0242       |

Von Wendt<sup>34</sup> has reported six metabolism experiments, covering thirty-five days, in which the income and outgo of iron was determined. He estimates that an average mixed diet will contain from 20 to 30 mg. of iron. His results are presented in Table 6.

TABLE 6.—IRON METABOLISM IN VON WENDT'S CASES

| Experiment<br>No. | Iron in Food<br>gm. | Iron in Feces<br>gm. | Iron in Urine<br>gm. | Balance<br>gm. |
|-------------------|---------------------|----------------------|----------------------|----------------|
| 1                 | 0.100               | 0.008                | 0.001                | + 0.001        |
| 2                 | 0.006               | 0.010                | 0.001                | — 0.005        |
| 3                 | 0.016               | 0.013                | 0.001                | + 0.002        |
| 4                 | 0.008               | 0.008                | 0.001                | — 0.001        |
| 5                 | 0.017               | 0.041                | 0.001                | — 0.025        |
| 6 (a)             | 0.016               | 0.015                | 0.001                | 0              |
| 6 (b)             | 0.007               | 0.015                | 0.001                | — 0.009        |

33. Stockman and Greig: Jour. Physiol., 1897, xxi, 55.

34. Von Wendt: Skand. Arch. Physiol., 1905, xvii, 211.

Sherman's results on the metabolism of iron are given in Table 7.

In closing, Sherman claims that the amount of iron metabolized in the body so as to be eliminated, in health is small, in fasting experiments 7 or 8 mg.; in metabolism experiments with restricted diets from 5.5 to 12.5 mg. per day, and that the amount of food-iron required for the maintenance of the equilibrium in healthy men lies between 6 and 12 mg. per day.

TABLE 7.—IRON METABOLISM

| Experiment No. | Iron in Food daily | Iron in Feces daily | Iron in Urine daily | Balance daily |
|----------------|--------------------|---------------------|---------------------|---------------|
| 1              | 0.0057             | 0.0053              | 0.0002              | + 0.0002      |
| 2              | 0.0065             | 0.0085              | 0.0002              | — 0.0022      |
| 3              | 0.0071             | 0.0124              | 0.0002              | — 0.0055      |

At present, since the work of Neumann<sup>35</sup> and of Neumann and Mayer,<sup>36</sup> about 1 mg. of iron, in the urine, for a period of twenty-four hours, is considered the normal output. In diseases of the blood, the following results have been obtained as regards the urinary excretion of iron. Zander<sup>37</sup> claims to have found a decided decrease in the urinary iron in chloranemia. Quincke,<sup>37</sup> however, showed that the excretion of iron was increased in the beginning of the disease, while later there was a lessened excretion. Lehmann<sup>37</sup> also found an increased excretion. Hunter<sup>38</sup> and Jolles and Winkler<sup>39</sup> have reported marked reductions in the urinary excretion of iron in chloranemia. Hunter<sup>40</sup> found a marked increase in the excretion of iron in pernicious anemia, at one time 32.26 mg. were excreted daily in the urine. Damaskin,<sup>31</sup> in pernicious anemia, reported an increased excretion, while Hopkins<sup>41</sup> found the excretion varied from traces to 8.3 mg. per day. In leukemia, an increased excretion of iron has also been found.<sup>42</sup> On comparing the results obtained as regards the iron metabolism in the study of this case of hemolytic jaundice with splenomegaly, with the results summarized above, it can readily be noted that there is a marked increase in the excretion of urinary and fecal iron, as would be

35. Neumann: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 114.

36. Neumann and Mayer: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 2 and 143.

37. Cited from Kennerknecht: *Virchow's Arch. f. path. Anat.*, 1911, ccv, 89 (contains the literature).

38. Hunter: *Brit. Med. Jour.*, 1890, ii, 1.

39. Jolles and Winkler: *Arch. f. exper. Path. u. Pharm.*, 1900, xlv, 464.

40. Hunter: *Practitioner*, 1889, xliii, 161, 321, 401.

41. Hopkins: *Guys Hosp. Reports*, 1894, vii, 373.

42. Hoffmann: *Zeit. f. anal. Chem.*, 1901, lxxiv, 40.

expected in a disease in which we have a hemolytic jaundice combined with an increased fragility of the red cells, and that the increased excretion is due to the liberation of the iron from the broken-down red cell.

TABLE 8.—THE FAT METABOLISM \*

|   | Date<br>12/10-12/14 |
|---|---------------------|
| Fat (gm.) in feces.....                     | 18.0                |
| Per cent. of fat in dried stool.....        | 26.2                |
| Per cent. of fat intake .....               | 9.1                 |
| Per cent. of fat absorbed .....             | 90.9                |
| Intake of fat (gm.).....                    | 165                 |
| Per cent. of neutral fat in stool fat. .... | 37                  |
| Per cent. of fatty acid in stool fat.....   | 27                  |
| Per cent. of soaps in stool fat.....        | 36                  |

\* Cholesterol not included.

*Discussion of Table 8.*—The fat metabolism is normal in character, with an absorption of 90.9 per cent. of the ingested fat. The amount of neutral fat, fatty acids and soap in the stool is normal, thereby excluding this as the cause for the loss of the calcium and magnesium

TABLE 9.—TESTS OF URINE AND FECES FOR UROBILIN, UROBILINOGEN, BILIRUBIN AND HEMOGLOBIN \*\*

| Date  | Urine     |               |            |             | Feces     |            |             |
|-------|-----------|---------------|------------|-------------|-----------|------------|-------------|
|       | Urobilin* | Urobilinogen* | Bilirubin† | Hemoglobin‡ | Urobilin: | Bilirubin: | Hemoglobin§ |
| 12/ 6 | 0         | +             | 0          | 0           | +         | 0          | 0           |
| 12/ 8 | +         | +             | 0          | 0           | +         | 0          | 0           |
| 12/10 | 0         | +             | 0          | 0           | +         | 0          | 0           |
| 12/11 | +         | +             | 0          | 0           | +         | 0          | 0           |
| 12/12 | 0         | 0             | 0          | 0           | +         | 0          | 0           |
| 12/13 | +         | +             | 0          | 0           | +         | 0          | 0           |
| 12/14 | +         | +             | 0          | 0           | +         | 0          | 0           |
| 12/15 | +         | +             | 0          | 0           | +         | 0          | 0           |
| 12/16 | +         | +             | 0          | 0           | +         | 0          | 0           |

\* Dimethylamidobenzaldehyd and spectroscopic tests used.

† Nakayamas and Gmelin's tests used.

‡ Schmidt's test used.

§ Spectroscopic and benzidine tests.

\*\* In this table the sign + stands for present and 0 for absent.

*Discussion of Table 9.*—Although urobilin is present in the urine normally, in small quantities, its presence cannot be detected by the tests used. A positive reaction with Ehrlich aldehyd reagent or with Schlesinger's zinc acetate test usually means that there has been either an abnormal destruction of red blood-cells or an insufficiency of the liver to perform its normal function.<sup>43</sup> We think, therefore, that the marked reaction for urobilin in the feces and urine of our case may be taken as an indication of the increased hemolysis present in this condition. In the case studied by McPhedran and Orr,<sup>44</sup> they found six times as much urobilin in the feces as in the stools of a normal control. Moller<sup>45</sup> found also that the total urobilin excretion in the urine and feces is greatly increased (400 mg. in twenty-four hours). It may also be noted that blood and bile pigments were absent from the urine and feces.

#### V. SUMMARY

1. A case of congenital hemolytic jaundice with splenomegaly and increased fragility of the red cells is described together with a metabolism experiment.

2. In a metabolism experiment of five days, there was a loss of 4.06 gm. of nitrogen, while the urinary nitrogen partition is normal in character with the exception of the uric acid nitrogen, which is increased. The absorption of nitrogen was normal.

3. The urinary sulphur partition is normal in character with occasional increased excretions of ethereal sulphates. In the five days there was a loss of 1.88 gm. of sulphur.

4. In the five days there was a loss of 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., while the amounts of earthy phosphates and total phosphates may be considered normal.

5. There was a loss of 0.1199 gm. of iron in the five days, with marked increased amounts of iron excreted in the urine and feces.

6. The fat metabolism was normal, with an absorption of about 91 per cent. of the ingested fat. The amounts of neutral fat, fatty acids and soaps in the stool were normal.

7. Urobilin and urobilinogen were present in the urine and feces. Bilirubin and hemoglobin were absent from the urine and feces.

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43. For a complete discussion of urobilin see Wilbur and Addis: *Urobilin: Its Clinical Significance*, THE ARCHIVES INT. MED., 1914, xiii, 235.

44. McPhedran and Orr: *Canad. Med. Jour. Assn.*, 1913, iii, 14.

45. Moller: *Berl. klin. Wchnschr.*, 1908, xlv, 1639.