TOXIC JAUNDICE IN PATIENTS UNDER ANTI-SYPHILITIC TREATMENT

A STUDY OF THE CHEMICAL ANALYSES OF THE BLOOD AND URINE, AND
OBSERVATIONS ON THE EFFECT OF EXERCISE AND DIET
IN THE TREATMENT OF SYPHILIS *

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The treatment of syphilis by injections of arsenobenzol derivatives is, at times, accompanied by more or less grave signs of intoxication. Of these, three distinct types seem to arise. In the first type, symptoms of general malaise shortly follow the administration of the drug and, as a rule, pass off within twenty-four hours. In the second and third types, toxic symptoms may be delayed and not appear until several months after the cessation of treatment. The most pronounced symptoms are associated with the skin or liver.¹ The skin lesion usually develops in the course of the treatment as a maculopapular eruption with considerable thickening. This rapidly becomes generalized. Desquamation is profuse, leaving a thickened, cyanosed and frequently pigmented surface. Pustulation is common. The patient becomes debilitated and has a slight fever. The liver and spleen are frequently enlarged. The urine shows a trace of protein and bile pigment. Patients whose liver symptoms predominate may pass several weeks in apparently good health following their course of treatment, and then come under observation with general malaise and jaundice. The latter, at first slight, becomes more pronounced. The liver, and frequently the spleen, becomes enlarged and tender. The blood pressure, pulse and temperature are usually low. Symptoms as in acute yellow atrophy of the liver may supervene,² or the patient may slowly convalesce.

A jaundice of the above type, occurring during the secondary stage of syphilis, has frequently been described. Rolleston,³ reviewing the literature on this subject, points out that this condition has frequently arisen in untreated cases and is not necessarily due to medication. Such cases improve under antisypilitic treatment. The cases

* From the Laboratory of Pathology, Ontario Military (No. 16 Canadian General) Hospital, Orpington, Kent.

1. Harrison, L. W.: *Quart. J. Med.* **10**:291 (July) 1917.

2. Willcox, W. H.: *Lancet* **1**:869 (May 24) 1919.

3. Rolleston, Sir Humphry: *Diseases of the Liver, Gallbladder and Bile Ducts*, London, 1912.

recognized as arsphenamin poisoning, on the other hand, are greatly aggravated by treatment. Untreated cases, in which jaundice and its associated signs occur coincidentally with the syphilitic skin lesions, bear a marked resemblance to many of the arsphenamin cases in which a mild jaundice is associated with severe dermatitis. It is possible that the arsenic in these cases simply accentuates a reaction which, to a mild degree, is ordinarily present in syphilis.

PREVENTIVE MEASURES

Unfortunately, the susceptible patients cannot be recognized, and, in spite of all precautions, the first intimation of trouble is the onset of the severe toxic symptoms. Of precautionary measures in administering treatment, the examination of the urine for signs of nephritis is recommended.⁴ Few of the cases, however, show such signs, and, on the whole, the kidneys are impaired but slightly, if at all. Testing the urine for bile pigment is equally of little use as the warning does not come in time. Of greater value in determining the state of jaundice is the test for bile pigment in the blood serum or plasma, and for this Gmelin's test is quite satisfactory.⁵ It is generally conceded that the development of any untoward symptom in the course of treatment should be considered carefully before further injections are given. The size and frequency of the dose have both been reduced greatly; Willcox and Webster⁶ recommend 0.3 gm. of arsphenamin or similar preparations (which is half the original dose) and the interval between doses to be two or three weeks. In using full doses (0.6 gm.), they recommend an interval of four weeks between injections. These intervals permit a complete elimination of the arsenic before a succeeding dose is given. Harrison,¹ referring to the cumulative effect of these remedies, states that "patients who have shown the most toxic effects have, in the majority of instances, done so after a number of doses have been administered." In a number of his cases, in which the intervals between treatments was sufficiently long to permit the excretion of all the arsenic, toxic symptoms developed after several treatments. He suggests that each succeeding dose contributes its quota to the damage, and finally definite toxic symptoms are precipitated by a final dose.

4. See Reference 23.

5. Considering that bilirubin is frequently found in the plasma of apparently healthy individuals, its determination by chemical methods is of little diagnostic value. Its repeated quantitative estimation in a particular case is an aid in following the course of the illness. The quantitative method described by Blankenhorn is of value in this respect. Blankenhorn, M. A.: *Tr. A. Am. Phys.*, 1917.

6. Willcox, W. H., and Webster, J.: *Brit. M. J.* **1**:473 (April 1) 1916.

Conditions similar to acute yellow atrophy of the liver have frequently been observed following combined mercurial and arsenical treatment,⁷ and it is of interest to recall that such symptoms have followed mercury alone.⁸ In selecting the dose of arsenic in these cases, the added toxic factor of the mercury must be considered. As a preventive of immediate toxic symptoms, Westrope⁹ reports favorable results from the use of a milk diet for twenty-four hours before the injection of the drug.

EXAMINATION OF CASES

An opportunity was afforded of making a chemical examination of the blood and urine in twenty-five cases of toxic jaundice following antisyphilitic treatment, and in fifteen cases convalescent or recovered from other illnesses. At the time of the examinations, the patients had shown toxic symptoms for periods ranging from 16 to 136 days; the majority were still slightly debilitated, others had apparently recovered. Six had bile pigment in the urine. None of the patients had proteinuria or other sign of nephritis, although in some cases the clinical history indicated that such symptoms had been present in the course of the illness. The antisyphilitic treatment in these cases consisted of an intravenous injection of novarsenobenzol (Billon) and a synchronous intramuscular injection of mercury, the doses being repeated at intervals of seven days.

CASE HISTORIES

CASE 1.—Male, aged 55; weight 116 pounds; no history of previous illness or infection.

October, 1918: Weakness, precordial pain and palpitation.

June 27, 1919: General weakness; liver 5 inches below costal margin; spleen, enlarged; blood pressure, 122/72; temperature, normal; hemoglobin, 53 per cent.; red cells, 3,736,000; Wassermann, +++.

Diagnosis.—Syphilitic hepatitis.

CASE 2.—Male, aged 23; weight 158 pounds. March 7, 1919: Exposure; sore discovered on penis the following day. Received novarsenobillon, 1.05 gm. and mercury, 0.128 gm., in two treatments with an interval of seven days. Following the second treatment he developed "swelling of the face" and nausea. He later became jaundiced.

April 4: Urine contained a trace of protein and bile pigment.

May 11: Well-marked icterus; liver at costal margin; spleen, not palpable; blood pressure, 130/80.

June 13: No arsenic found in urine seventy-four days after last treatment.

June 20: Urine constantly contained bile pigment, at times a trace of protein and on one examination tyrosin. He has never given a positive Wassermann reaction.

June 27: Chemical blood analysis. Clinical findings negative.

7. Severin: *Ztschr. klin. Med.* **76**:138, 1912; Bedig: *Münch. med. Wchnschr.* **62**:1140, 1915.

8. Tileston, W.: *Boston M. & S. J.* **158**:510, 1908.

9. Westrope: *Brit. M. J.* **2**:456, 1916.

CASE 3.—Male, aged 24; weight, 155 pounds. Jan. 25, 1919: Chancre.

March 6: Combined treatment instituted; received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with seven day intervals. Following the fifth treatment, nausea and jaundice developed.

May 11: Slight icterus; liver 1 inch below costal margin; urine showed a trace of protein, no bile pigment, leucin, tyrosin of bile salts.

June 17: No arsenic found in urine fifty-two days after last treatment.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 4.—Male, aged 34; weight, 146 pounds. Dec. 26, 1918: Chancre.

March 30, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with seven day intervals. He became ill and jaundiced after the last injections.

May 11: Marked jaundice, liver, 1.5 inch below costal margin; spleen, slightly enlarged; blood pressure, 128/86. Bile pigment in urine, no protein, leucin or tyrosin.

June 13: No arsenic found in urine seventy-one days after last injection.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 5.—Male, aged 24; weight, 134 pounds. Jan. 1, 1919: Chancre.

March 8, 1919: Had received novarsenobillon, 4.65 gm., and mercury, 0.518 gm., in eight treatments with intervals of seven days.

May 14: Jaundice developed.

May 20: Slightly jaundiced; pupils unequal, liver tender and 1½ inch below costal margin; spleen not palpable; blood pressure, 128/80. Urine contains a trace of bile pigment; no protein.

June 13: No arsenic found in urine ninety-three days after last injection.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 6.—Male, aged 24; weight, 150 pounds. July, 1917: Received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Following this he was somewhat debilitated. These treatments were repeated in October, 1918, and again in January, 1919. In May, 1919, he had an abscess of the left buttock associated with severe generalized furunculosis and great weakness. Liver was tender and 1½ inch below costal margin. Spleen, palpable. Wassermann, negative. Urine, contained a trace of bile pigment; no protein. Blood pressure, 110/67.

June 17: No arsenic found in urine 117 days after last injection.

July 1: Chemical blood analysis. Abscesses healed. Debilitated.

CASE 7.—Male, aged 20; weight 155 pounds. March 20 1919: Chancre.

May 8, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.388 gm., in six treatments with intervals of seven days. Following the fourth injection he became febrile, and following the sixth injection he developed anorexia, jaundice and constipation; later, diarrhea.

May 24: Diarrhea; sclera jaundiced; skin clear; liver, palpable and tender; blood pressure, 100/65. Wassermann, negative.

June 13: Repeated urinalysis showed nothing abnormal. No arsenic found in urine thirty-six days after last injection.

July 1: Greatly improved. Chemical blood analysis.

CASE 8.—Male, aged 42; weight, 163 pounds. Dec. 5, 1918: Chancre.

Feb. 4, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Eleven days after the last injection, he developed pains in the chest and abdomen, weakness and constipation. Liver, 1½ inch below costal margin; spleen, palpable; Wassermann, negative; urinalysis, normal.

May 7. Apparently recovered. Given seven days' leave.

May 14: Returned markedly jaundiced, complaining of anorexia, weakness and a "distended feeling" in the liver region. Liver, $1\frac{1}{2}$ inch below costal margin; tender. Urine contained a large amount of bile pigment; no protein. Wassermann, negative.

June 13: Urine free from bile pigment, protein, leucin, tyrosin and bile salts. No arsenic found in the urine 129 days after last injection.

July 1: Chemical blood analysis. Skin still discolored and he suffered from slight debility.

CASE 9.—Male, aged 33; weight, 147 pounds. January, 1919: Chancre.

April 8, 1919: Had received novarsenobillon, 1.65 gm., and mercury, 0.194 gm., in three treatments with intervals of seven days. He became jaundiced after the last injection. Wassermann, negative.

May 22: Thin, distinctly jaundiced; liver, 1 inch below costal margin. Blood pressure, 108/70. Urine contained bile pigment; no protein.

June 13: No arsenic found in the urine sixty-seven days after the last injection. Aug. 1: Chemical blood analysis. Slightly debilitated.

CASE 10.—Male, aged 31; weight, 137 pounds. Jan. 23, 1919: Chancre.

April 10, 1919: Had received novarsenobillon, 5.1 gm., and mercury, 0.58 gm., in nine treatments with intervals of seven days. April 23: Slight jaundice; gingivitis; ulceration of left cheek; weakness. Liver, tender, 2 inches below costal margin. Spleen, enlarged. Urinalysis, negative. No arsenic found in urine fifty-six days after last injection.

August 1: Chemical blood analysis. Jaundice had disappeared; liver and spleen were greatly reduced in size, and he had no complaints.

CASE 11.—Male, aged 34; weight, 136 pounds. November, 1918: Chancre.

December-January, 1919: Received novarsenobillon, 4.05 gm., and mercury, 0.5 gm., in seven treatments with intervals of seven days.

April 15, 1919: Anorexia, nausea and jaundice.

May 1: Slight debility; moderately jaundiced; blood pressure, 112/78. No arsenic found in the urine 157 days after the last injection.

July 7: Chemical blood analysis. Liver had not decreased in size; otherwise his clinical findings were negative.

CASE 12.—Male, aged 32; weight, 146 pounds. Ulcer on penis in 1911, for which he took pills for a period of eight weeks. Gassed in September, 1918. February, 1919: Urethritis; four weeks' treatment.

March 7, 1919: Received one injection of novarsenobillon, 0.45 gm.; furuncles appeared on legs and treatment was stopped.

April 26: Severe generalized dermatitis. Liver $2\frac{1}{2}$ inches below costal margin. Spleen enlarged. Urine contained bile pigment. Wassermann, negative. No arsenic found in urine 125 days after last injection.

August 7: Chemical blood analysis. The liver and spleen had not decreased in size, the former, however, had lost its tenderness. The skin lesions had cleared up and he had no complaints.

CASE 13.—Male, aged 29; weight, 144 pounds. December, 1915: Chancre.

February, 1916: Received three injections of arsphenamin.

June, 1916: Developed a second sore on penis. Received arsphenamin, 5.95 gm., and mercury, 0.64 gm., in ten treatments ending in September, 1917. Late in September, he developed nausea, vomiting, and general debility, necessitating six weeks hospital treatment.

January, 1919: Wassermann strongly positive. He received novarsenobillon, 2.25 gm., and mercury, 0.26 gm., in four treatments with intervals of seven days.

May 2: Headache, coated tongue, constipation and jaundice. Liver $1\frac{1}{2}$ inch below costal margin. Spleen, not palpable. Blood pressure, 115/80. Urine contained a trace of protein and bile pigment.

June 13: Urine free from protein, bile pigment, leucin, tyrosin and bile salts. No arsenic was found in the urine ninety days after the last injection.

July 7: Chemical blood analysis. General condition had improved. Urine free from protein and bile pigment for two months. Liver and spleen still enlarged.

CASE 14.—Male, aged 23; weight, 138 pounds. October, 1918: Chancre. Received novarsenobillon, 4.65 gm., and mercury, 0.5 gm., in eight treatments with intervals of seven days, terminating Dec. 28, 1918.

April 28, 1919: Anorexia, followed in one week by pain in the liver region and jaundice.

May 10: Anorexia, constipation and jaundice. Liver, tender, $1\frac{1}{2}$ inch below costal margin. Spleen, slightly enlarged. Blood pressure, 115/62. Urine contained bile pigment.

June 7: Jaundice disappeared. No arsenic found in the urine 180 days after last injection.

July 7: Chemical blood analysis. General condition had greatly improved; liver and spleen slightly decreased in size.

CASE 15.—Male, aged 22; weight, 135 pounds. February, 1916: Nephritis; ill eight months; recurrences in July, 1917, and May, 1918. February, 1919: Chancre.

March 4, 1919: Combined treatment instituted. Received novarsenobillon, 2.95 gm., and mercury, 0.324 gm., in five treatments with intervals of seven days. Nephritic symptoms developed.

May 14: Liver and spleen not palpable. Blood pressure, 125/80. No complaints. Urine contains a trace of bile pigment, protein and an occasional hyalin and granular cast.

August 7: Chemical blood analysis. Free from symptoms. Wassermann, negative.

CASE 16.—Male, aged 20; weight, 137 pounds. December, 1918: Chancre.

Feb. 14, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

May 10: Severe abdominal pains, followed by slight jaundice.

May 15: Slightly jaundiced; liver, palpable, not tender; spleen, not palpable. Blood pressure, 128/80. Urine contains a trace of protein and bile pigment; no bile salts or casts. Wassermann, negative. No arsenic found in urine eighty-eight days after last injection.

August 7: Chemical blood analysis. Jaundice had disappeared, liver was at costal margin, and he had no complaints.

CASE 17.—Male, aged 24. Jan. 1, 1919: Chancre.

April 4: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Following the third treatment, general malaise. Following the sixth treatment, severe dermatitis, which became greatly aggravated following the seventh and last treatment.

April 10: Marked gingivitis, stomatitis and purulent conjunctivitis. Skin brawny red with copper colored papules. Marked exfoliation. Blood pressure, 115/80. Liver not palpable. Urine contains bile pigment, protein, cholesterol, a few red blood cells and granular casts.

April 25: Liver 2 inches below costal margin. Spleen, enlarged. Dermatitis improving.

June 6: Urine contains bile salts; no bile pigment. August 13: Chemical blood analysis. General condition had greatly improved. The skin remained thickened and there was a slight desquamation. Liver and spleen had decreased in size. Wassermann, negative.

CASE 18.—Male, aged 23. Feb. 7, 1919: Chancre.

March 14, 1919: Had received novarsenobillon, 2.85 gm., and mercury, 0.32 gm., in five treatments with intervals of seven days. March 20: Developed a severe dermatitis. April 10: Skin thickened, purplish red, with a fine papular

eruption and marked scaly exfoliation. Moderate stomatitis and conjunctivitis. Liver and spleen not palpable. Blood pressure, 100/60. Urine contains bile pigment and salts; no leucin or tyrosin.

April 25: Liver 1 inch below costal margin. White blood cells, 17,200. Temperature, from 99 to 100 F.

May 9: Spleen, palpable.

July 13: Chemical blood analysis. Recovered from dermatitis. Liver and spleen still palpable. Wassermann, negative. Urine contained no arsenic ninety-one days after last injection.

CASE 19.—Male, aged 36. Received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days, the course terminating in April, 1919. No immediate reaction. Wassermann, negative.

May 29, 1919: Returned from seven days' leave complaining of drowsiness, anorexia, nausea, clay colored stools and jaundice.

July 2: Markedly jaundiced; liver, palpable; tenderness over gallbladder. Urine contained bile pigment, a trace of protein and an occasional granular cast. No arsenic found in urine seventy-five days after last injection.

July 13: Chemical blood analysis. Clinical findings remained unchanged, excepting for the absence of protein and casts in the urine.

CASE 20.—Male, aged 21. Typhoid, 1910. Gonorrheal urethritis and prostatitis, February to May, 1919.

June 24, 1919: Weakness, nausea and jaundice. Liver and spleen palpable.

July 13: Chemical blood analysis. Jaundice and subjective symptoms had disappeared. Liver and spleen still palpable.

CASE 21.—Male, aged 27. Psoriasis. April 20, 1919: Chancre.

June 11, 1919: Had received novarsenobillon, 3.45 gm., mercury, 0.32 gm., in seven treatments with intervals of seven days. Following the third injection, chills, headache and muscular stiffness; following the fourth injection, a maculopapular eruption.

June 25: Marked generalized dermatitis with profuse desquamation. Liver, 1½ inch below costal margin. Wassermann, negative. No arsenic found in urine thirty-two days after last injection.

July 13: Chemical blood analysis. Clinical findings unchanged.

CASE 22.—Male, aged 37. Dec. 15, 1918: Chancre.

Jan. 29, 1919: Had received novarsenobillon, 3.45 gm., and mercury, 0.388 gm., in six treatments with intervals of seven days. Following the fifth treatment an eruption appeared on the neck.

March 31: Wassermann, negative. A trace of protein in the urine.

April 12: Moderate conjunctivitis, skin red, with diffuse dark papules, slight desquamation. Liver, palpable. Blood pressure, 96/60. Urine contains a trace of bile pigment and protein.

April 25: Marked generalized desquamation. Liver, 2 inches below costal margin. Spleen, enlarged. Several abscesses on thighs and neck. No trace of arsenic in 50 gm. of skin flakes.

May 16: Abscesses healed. Desquamation slight. Skin markedly pigmented. Blood pressure, 125/80. Liver and spleen as before. Temperature, from 99 to 103 F. for past three weeks. Complains of numbness in feet. White blood cells, 14,000.

June 9: Urine free from bile pigment, bile salts, protein, leucin, tyrosin and casts. Wassermann, negative. No arsenic found in urine 135 days after last injection.

July 17: Chemical blood analysis. General condition greatly improved.

CASE 23.—Male, aged 23. Feb. 27, 1919: Chancre.

May 5, 1919: Had received novarsenobillon, 2.85 gm., and mercury, 0.32 gm., in five treatments with intervals of seven days. This was immediately followed by a severe generalized dermatitis, associated with marked desquamation and numerous small abscesses. Urine contained a trace of protein.

April 25: Deep pigmentation of skin; fine branny desquamation. Liver and spleen enlarged. Blood pressure, 115/70. Loss of finger nails. Urinalysis normal. No arsenic found in urine seventy-four days after last injection. July 17: Chemical blood analysis. General condition improving; still a bed patient.

CASE 24.—Male, aged 22. June 13, 1919: Deeply jaundiced. Urine contains bile pigment, protein and granular casts. No history of syphilis or of treatment.

July 2, 1919: Deeply jaundiced, liver and spleen palpable; indefinite pains in liver region; stools clay colored; appetite, good; Wassermann, negative.

August 17: Chemical blood analysis. Condition unchanged, excepting for the absence of protein and casts in the urine.

CASE 25.—Male, aged 21; weight, 160 pounds. Feb. 12, 1919: Had received novarsenobillon, 5.45 gm., and mercury, 0.648 gm., in ten treatments with intervals of seven days.

August 1: Anorexia, nausea and jaundice. Liver and spleen not enlarged. Urine contains bile pigment and bile salts. No arsenic found in urine 125 days after last injection.

August 17: Chemical blood analysis. General condition fair; slightly jaundiced; liver not enlarged.

CASE 26.—Male, aged 21. April 21, 1919: Chancre.

June 12, 1919: Had received novarsenobillon, 6.4 gm., and mercury, 0.71 gm., in eleven treatments with intervals of seven days.

June 29: Chills, weakness, abdominal cramps, constipation and jaundice. Wassermann, negative.

July 7: Complaints of weakness; jaundice persists; liver, palpable. No arsenic found in urine thirty-five days after last injection.

July 17: Chemical blood analysis. Condition unchanged.

CASE 27.—Male, aged 25. Feb. 9, 1919: Chancre.

March 17, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

June 13: Weakness, constipation and jaundice.

July 8: Deeply jaundiced. Liver, slightly enlarged. No arsenic found in urine ninety days after last injection.

July 17: Chemical blood analysis. General condition slightly improved.

CASE 28.—Male, aged 34. No history of infection. April 10, 1919: Developed a generalized maculopapular eruption. Wassermann, strongly positive.

June 23, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

June 27: Nausea, vomiting and jaundice.

July 8: Jaundiced; liver, palpable; urine contains bile pigment; no complaints. No arsenic found in urine twenty-four days after last injection.

July 17: Chemical blood analysis. General condition unchanged.

CASES 29 to 34.—These patients were recovering from illnesses other than toxic jaundice, and at the time of the chemical blood analyses were still in a weakened condition.

CASES 35 to 40.—These men were apparently in good health at the time of the chemical blood analyses.

METHODS EMPLOYED

A complete twenty-four hour specimen of urine was collected from each patient on the day preceding the blood analysis. On these specimens were determined the volume, reaction, specific gravity, protein, sugar, bilirubin, bile salts, urobilinogen, urobilin, uric acid and the microscopic contents.

Synchronous blood and urine specimens were collected on the following morning before breakfast, by the following method: At 6 a. m. the patient completely emptied his bladder; at 7:30 a. m., from 30 to 40 c.c. of blood was aspirated, by venipuncture, into a bottle containing potassium oxalate crystals (20 drops of 20 per cent. potassium oxalate solution evaporated on the bottom and sides of the bottle); at 9 a. m., the three-hour specimen of urine was collected. In some cases, when the urinary excretion was low, a glass of water was given during this period.

The following estimations were made on the whole blood: Sugar, creatinin, cholesterol, urea nitrogen, uric acid and bile salts. Bilirubin tests were made on the plasma.

On the three hour specimens of urine, the following determinations were made: Rate of excretion, reaction, specific gravity; the presence of bile salts and protein, and, quantitatively, sugar, uric acid, urobilinogen, urobilin and bilirubin.

Sugar in the urine was estimated quantitatively by Myers' method,¹⁰ bilirubin, by Hooper and Whipple's modification of Huppert's reaction;¹¹ bile salts were estimated by Hay's sulphur test. Urobilinogen was tested by extracting with amyl alcohol after developing the color in the urine by the use of Ehrlich's reagent; diluting to a suitable volume with amyl alcohol, and obtaining relative quantitative figures by matching against a standard solution in a Hellige colorimeter. The relative rate of excretion was obtained by multiplying this figure by the c.c. per hour of urine and dividing by 1,000.

Urobilin estimations in the urine were made by extracting with amyl alcohol and adding to this an ammoniacal alcoholic solution of zinc chlorid; relative quantitative figures were obtained by repeated alcoholic dilutions until no fluorescence could be detected on examining in sunlight against a black background. The relative rate of excretion was obtained by multiplying the dilution by the c.c. per hour of urine and dividing by 100. The relative oxidation of urobilinogen was obtained by dividing urobilin by urobilinogen. Uric acid in the urine was quantitatively determined by the method of Benedict and Hitchcock.¹² Blood sugar estimations were made by a modification of the Lewis and Benedict method.¹³

Creatinin in the blood was estimated by Folin's method as modified and described by Myers and Killian.¹⁴ Blood cholesterol was deter-

10. Myers, V. C.: *Proc. Soc. Exper. Biol. & Med.* **13**:178, 1916.

11. Hooper, C. W., and Whipple, G. H.: *Am. J. Physiol.* **40**:332, 1916.

12. Benedict, S. R., and Hitchcock, E. H.: *J. Biol. Chem.* **20**:619, 1915.

13. Myers, V. C., and Bailey, C. V.: *J. Biol. Chem.* **24**:147, 1915.

14. Myers, V. C., and Killian, J. A.: *Am. J. M. Sc.* **157**:674, 1919.

mined by the method described by Myers and Wardell,¹⁵ urea nitrogen in the blood, by Van Slyke and Cullen's modification of Marshall's method;¹⁶ uric acid in the blood, by the Folin and Denis-Benedict method as described by Myers and Fine.¹⁷

The presence of bile salts in the blood was determined by applying Pettenkofer's test to the supernatant fluid, after the precipitation of the purins, in the method for estimating the blood uric acid; 10 c.c. of blood was used in this test. Gmelin's test for bilirubin was applied directly to the plasma. Bilirubin in the plasma was also estimated by the method described by Blankenhorn⁵ and found to correspond with the results of Gmelin's test. The method consists in diluting the plasma until a color can barely be detected in a column 1 cm. deep; the number of dilutions is the bilirubin index.

A modified Gutzeit's test¹⁸ was used for arsenic, 50 c.c. of urine being employed.

DISCUSSION

Excretion of Arsenic.—No arsenic was found in the urine of any of these patients; tests were made at periods varying from 24 to 157 days after the last treatment.

Analyses of Twenty-Four-Hour Urines.—The twenty-four-hour urines of all these patients were free from protein and pathologic sediment. No bile salt was indicated by Hay's test. Six of the patients clinically jaundiced had bile pigment in the urine; the method used was found unsuitable for accurate quantitative determination of small quantities.

The relative rate of excretion of urobilinogen and the relative oxidation of this substance to urobilin are shown in Table 1, and will be referred to later. The daily excretion of sugar is shown in Table 1 to be normal in all of the cases¹⁹—the amount not being detectable by ordinary methods. The daily excretion of uric acid was much greater in the more severe cases.

Bilirubin, Urobilinogen, Urobilin.—In eleven cases, bile pigment was found in the plasma and, as a rule, in these cases bile salts were also found, although a few cases showed dissociation. The extent of the jaundice did not correspond with the severity of the illness.

In Table 3 the cases are grouped according to the presence or absence of bilirubin in the plasma; cases not associated with disordered liver are classified by the presence or absence of debility. The greatest

15. Myers, V. C., and Wardell, E. L.: J. Biol. Chem. **36**:147, 1918.

16. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **19**:211, 1914.

17. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **20**:391, 1915.

18. Simon, W.: Manual of Chemistry, New York, 1916.

19. Bailey, C. V.: Arch. Int. Med. **23**:455 (Oct.) 1919.

excretion of urobilinogen and urobilin was noted in the jaundiced cases; in the liver cases which were free from jaundice the output of this pigment was less than half. Among the cases not associated with liver disturbance, the debilitated patients had twice the excretion of the well patients. A relatively higher rate of excretion of urobilinogen and urobilin was present in the early morning than, on the average, during the day. This was most marked in the severe cases, the early morning rate being 19.66 per hour, while for the twenty-four-hour period the rate was 13.4 per hour. The difference in the liver cases in which improvement was noted was less marked, being 8.6 per hour in the morning and 7.6 per hour in the twenty-four-hour specimens.

TABLE 1.—TWENTY-FOUR-HOUR URINE

Case	Volume, C.c.	Bili- rubin	Total Relative Excretion		Relative Oxida- tion of Urobi- linogen	Uric Acid		Sugar, Gm. in 24 Hrs.
			Urobi- linogen	Urobilin		Gm. in 24 Hrs.	Mg. per Hr.	
1	2,300	—	565.8	20.7	0.04	0.65	27.0	1.61
2	2,210	—	165.75	24.31	0.15	0.975	40.62	1.69
3	1,260	—	191.52	10.08	0.05	0.945	39.37	1.33
4	1,325	—	250.42	19.87	0.08	0.903	37.62	1.67
5	1,495	—	55.31	17.94	0.32	0.57	23.75	1.02
6	1,005	—	55.27	11.05	0.2	0.65	27.0	1.18
7	1,424	—	148.09	249.2	1.68	0.726	30.25	1.28
8	1,480	—	325.6	22.2	0.07	0.518	21.58	1.48
9	1,120	—	259.8	20.72	0.08	0.683	28.45	1.32
10	1,520	—	161.12	9.12	0.06	0.744	31.0	2.55
11	1,150	—	188.6	63.25	0.34	0.57	23.75	1.28
12	1,600	—	54.4	16.0	0.29	0.48	20.0	0.67
13	2,350	—	65.8	18.8	0.28	0.607	25.29	1.63
14	1,450	—	79.75	26.1	0.33	0.75	31.25	0.84
15	2,150	—	75.25	217.15	2.85	0.47	19.58	0.73
16	660	—	192.06	27.06	0.14	0.56	23.33	0.9
17	1,300	—	54.6	16.9	0.31	1.35	56.25	1.17
18	1,150	—	138.0	33.35	0.24			1.56
19	2,315	+++	451.42	131.95	0.29			1.39
20	1,470	—	51.45	42.63	0.83	0.715	29.79	0.88
21	740	+	63.64	66.16	1.04			1.18
22	1,470	—	52.92	164.64	3.11	1.4	58.33	1.23
23	2,030	—	36.54	64.96	1.77	0.574	23.91	1.14
24	1,700	++	88.4	149.6	1.69	0.83	34.58	1.22
25	1,150	++++	414.0	146.0	0.35	1.1	45.83	2.76
26	1,050	—	25.2	115.5	4.58	0.743	30.95	1.28
27	1,800	++	594.0	273.6	0.47	1.75	72.91	2.41
28	1,470	++++	117.6	211.68	1.8	1.62	67.5	2.47

Oxidative Activity of the Urine.—In the voided urine, the relative oxidation of urobilinogen to urobilin was greatest in the well patients and least in the severe liver cases, indicating either the presence of a protecting substance or of a decreased excretion of oxidase in these cases. The latter is the probable explanation as in similar conditions—poisoning by phosphorus, chloroform, etc.—there is a decrease of oxidation in the body, as shown by the respiratory exchange and the presence of incompletely oxidized bodies in the urine.²⁰ In Table 3 the figures indicate not only a decreased excretion of oxidase in the liver cases, but also in debilitating conditions not clinically associated

20. Wells, H. G.: Chemical Pathology, Philadelphia and London, 1918, p. 542.

with disordered liver. Absolute rest seems to increase the excretion, and probably the production of oxidase; in the twenty-eight liver cases the oxidative activity in the urine was greater in the early morning than in the twenty-four-hour specimens in the proportion of 59 to 49.

Cholesterol.—Of greater interest is the concentration of cholesterol in the blood. In the twelve cases not associated with disordered liver, the percentage varied from 0.117 to 0.21, giving an average of 0.155 per cent., which compares favorably with Gorham and Myer's fourteen normal cases with an average of 0.15 per cent., using the same method.²¹ Of the patients with catarrhal jaundice, one (Case 20) had recovered and showed a blood cholesterol of 0.153 per cent.; a second patient (Case 24) was still deeply jaundiced and had a slight increase of this substance in his blood (0.184 per cent.). The blood cholesterol in the case of syphilitic hepatitis is slightly above the average normal. In the twenty-five cases of toxic jaundice, the cholesterol value is strikingly high, giving an average of 0.235 per cent., the values varying from 0.165 per cent. in a patient apparently recovered, to 0.292 per cent. in a recent case. In 84 per cent. of these cases, the value is over 0.2 per cent. In Table 3 one sees that the greatest concentration of cholesterol in the blood occurred in the cases in which bile pigment was found in the plasma. Hypercholesterolemia, however, was found in nearly all of the toxic cases and was present in the patients free from symptoms, while still under hospital treatment. It seems to be an early and marked sign of toxic jaundice and its presence may be a valuable sign of a precarious state of the liver in these cases.

Sugar.—No disturbance of carbohydrate metabolism was discovered. The values for blood sugar are normal; in the last six cases the values are above normal, but these patients were examined three hours after breakfast and were influenced by alimentation. The excretion of sugar at the time of the blood analyses and for the twenty-four-hour period was at the normal rate.¹⁹

Blood Urea and Creatinin.—A study of the nonprotein nitrogenous constituents of the blood is complicated by the high protein diets and the varying physical restrictions placed on these men. The values for urea nitrogen in the last six cases, the patients apparently being in good health, are within the upper normal limit, which is 20 mg. per hundred c.c. of blood.²² Of the remaining cases, some show normal values, but the majority are above normal, one as high as 49 mg. per hundred c.c. That this increase is in part due to impaired elimination by the kidneys is shown by the fact that, with few exceptions, the cases with a urea nitrogen exceeding 20 mg. per hundred show a slight

21. Gorham, F. D., and Myers, V. C.: *Arch. Int. Med.* **20**:599 (Nov.) 1917.

22. Kast, L., and Wardell, E. L.: *Arch. Int. Med.* **22**:581 (Nov.) 1918.

TABLE 2

Case	Day of Illness	Blood					Urine—						
		Bilirubin		Bile Salts	Cholesterol, per Cent.	Sugar, per Cent.	Gm. per 100 C.c.			Sugar, Gm. per Hr.	Uric Acid, Mg. per Hr.	Index of Uric Acid Excretion*	Bilirubin
		Gmelin's Test	By Dilution of Plasma				Creatinin	Urea N	Uric Acid				
1	239	—	...	—	0.171	0.086	2.2	40	4.41	0.06	23.86	0.18	—
2	92	—	...	—	0.165	0.102	2.85	22	4.9	0.046	20.87	0.23	—
3	81	—	...	—	0.263	0.1	2.6	32	3.3	0.06	25.88	0.127	—
4	89	—	...	—	0.279	0.09	2.4	33	4.7	0.036	28.56	0.17	—
5	13	—	...	—	0.233	0.118	3.2	37	4.2	0.036	9.08	0.466	—
6	55	—	16	+	0.208	0.096	1.98	22	3.67	0.056	32.2	0.114	—
7	54	—	8	—	0.203	0.102	1.94	24	2.11	0.044	43.1	0.049	—
8	136	—	12	—	0.233	0.1	1.96	27	2.46	0.015	8.21	0.3	—
9	84	+	30	—	0.267	0.11	2.22	24	3.7	0.035	19.2	0.2	—
10	69	—	12	—	0.193	0.1	2.1	23	3.57	0.044	28.11	0.127	—
11	83	+	24	—	0.292	0.118	2.5	31	2.5	0.054	19.3	0.13	—
12	122	—	14	—	0.275	0.106	2.4	43	3.87	0.234	10.13	0.387	—
13	66	—	10	—	0.205	0.112	2.6	30	3.57	0.066	63.5	0.056	—
14	70	—	10	—	0.203	0.092	2.26	28	5.0	0.046	27.8	0.178	—
15	90	—	14	—	0.212	0.1	2.58	31	4.78	0.147	66.0	0.072	—
16	58	—	14	—	0.203	0.108	2.02	33	1.76	0.056	22.6	0.076	—
17	113	—	8	—	0.258	0.094	2.41	15	4.34	0.069	96.7	0.045	—
18	85	—	12	—	0.175	0.096	1.76	12	5.55	0.033			—
19	45	+++	150	+	0.222	0.108	1.74	8	1.94	0.048	56.7	0.034	+++
20	19	++	60	—	0.153	0.108	1.54	11	3.12	0.032	20.5	0.156	—
21	45	++	40	+	0.292	0.096	1.8	14	5.31	0.034	60.5	0.087	+
22	170	—	12	—	0.285	0.124	2.13	14	5.0	0.045	44.6	0.11	—
23	74	+	50	+	0.17	0.12	2.8	30	3.0	0.07	44.6	0.066	—
24	34	+++	120	+	0.184	0.084	1.5	20	2.7	0.054	50.0	0.074	++
25	16	+++	80	+	0.24		1.8	36	6.3	0.2	168.6	0.037	++++
26	18	++	50	+	0.292		1.7	16	2.39	0.148	95.0	0.025	—
27	34	++	80	++	0.275		1.3	29	3.1	0.052	66.0	0.047	++
28	20	++	90	+++	0.237	0.116	1.2	39	1.5	0.055	53.4	0.028	++++
29	...	—	...	—	0.21	0.1	2.3	36	5.54	0.03	31.0	0.178	—
30	...	—	...	—	0.12	0.102	2.0	34	6.4	0.027	26.2	0.246	—
31	...	—	...	—	0.16	0.112	2.1	36	2.3	0.105	103.1	0.022	—
32	...	—	...	—	0.18	0.108	1.9	47	3.3	0.052	27.3	0.037	—
33	...	—	...	—	0.15	0.1	1.98	41	5.45	0.104	89.4	0.2	—
34	...	—	...	—	0.117	0.088	1.84	49	3.23	0.098	64.0	0.05	—
35	...	—	...	+	0.19	0.124	2.3	16	2.32	0.014	8.0	0.29	—
36	...	—	...	—	0.12	0.112	2.1	18	3.0	0.03	34.0	0.085	—
37	...	—	...	—	0.17	0.12	2.0	19	3.3	0.035	47.2	0.07	—
38	...	—	...	—	0.137	0.12	2.1	20	2.4	0.028	35.6	0.066	—
39	...	—	...	—	0.15	0.118	2.1	18	5.6	0.033	54.8	0.1	—
40	...	—	...	—	0.16	0.128	2.1	20	1.7	0.024	35.7	0.046	—

* Milligrams per 100 C.c. of blood divided by milligrams per hour excreted.

TABLE 2

—Urine			Diet					Diagnosis	Remarks
Relative Excretion Rate per Hr.		Relative Oxidation of Urobilinogen	Protein			Fat, Gm.	Carbohydrate, Gm.		
Urobilinogen	Urobilin		Animal, Gm.	Vegetable, Gm.	Total, Gm.				
52.64	2.24	0.04	90	60	150	152	435	Syphilitic hepatitis	Debilitated; unrestricted; up and about
3.18	0.73	0.23	90	60	150	152	435	Toxic jaundice	
1.37	0.66	0.48	90	60	150	152	435	Toxic jaundice	
3.68	0.80	0.22	90	60	150	152	435	Toxic jaundice	
1.85	1.46	0.79	90	60	150	152	435	Toxic jaundice	
4.94	1.25	0.25	82	59	141	106	450	Toxic jaundice and furunculosis	Confined to hospital ward
4.48	3.28	0.73	90	60	150	152	435	Toxic jaundice	
9.47	0.27	0.03	95	9	104	124	282	Toxic jaundice	
9.72	0.36	0.04	95	34	129	126	380	Toxic jaundice	
2.22	0.44	0.20	90	60	150	152	435	Toxic jaundice	
4.62	10.22	2.21	90	60	150	152	435	Toxic jaundice	Debilitated; unrestricted; up and about
1.07	3.04	2.84	99	60	150	152	435	Toxic jaundice and furunculosis	
4.08	2.52	0.63	90	60	150	152	435	Toxic jaundice	
4.66	8.68	1.73	90	60	150	152	435	Toxic jaundice	
11.54	7.35	0.64	90	60	150	152	435	Toxic jaundice and nephritis	
4.53	5.78	1.27	90	60	150	152	435	Toxic jaundice	Confined to hospital ward
16.25	5.31	0.33	123	35	158	147	366	Toxic jaundice and dermatitis	
8.8	4.24	0.48	123	35	158	147	366	Toxic jaundice and dermatitis	
33.28	3.45	0.10	72	53	125	105	392	Toxic jaundice	
2.34	4.75	2.03	98	37	135	132	414	Catarrhal jaundice	
7.68	6.92	0.90	117	33	150	35	386	Toxic jaundice and dermatitis	Confined to hospital ward
3.25	6.35	1.95	124	33	157	147	353	Toxic jaundice and dermatitis	
3.4	5.8	1.70	102	59	161	118	490	Toxic jaundice and dermatitis	
2.7	7.62	2.82	136	52	188	130	438	Catarrhal jaundice	
22.81	16.38	0.71	90	60	150	152	435	Toxic jaundice	
17.55	11.7	0.66	90	60	150	152	435	Toxic jaundice	Debilitated; unrestricted; up and about
12.94	7.0	0.54	109	80	189	162	643	Toxic jaundice	
20.44	4.6	0.22	115	80	195	164	643	Toxic jaundice	
1.45	1.86	1.28	90	60	150	152	435	Bronchitis	
1.33	5.06	3.80	90	60	150	152	435	Disordered action of the heart	
8.14	4.62	0.56	90	60	150	152	435	Meningitis	Debilitated; unrestricted; up and about
2.47	5.98	1.15	90	60	150	152	435	General debility	
5.2	11.90	4.84	90	60	150	152	435	Syphilis and tonsillitis	
10.92	4.62	0.42	90	60	150	152	435	Constipation	
0.53	1.18	2.23	90	60	150	152	435	Influenza	
1.06	1.12	1.06	90	60	150	152	435	Arthritis	Recovered; unrestricted; up and about
1.41	2.4	1.70	90	60	150	152	435	Gastritis	
1.17	2.68	2.29	90	60	150	152	435	Normal	
1.7	3.12	1.83	90	60	150	152	435	Sciatica	
1.19	1.93	1.62	98	53	151	133	429	Normal	

increase in blood creatinin and uric acid and a decreased excretion of uric acid as shown by the ratio of excretion to blood concentration. These patients were all more or less debilitated and their high protein diet probably accounts for most of the urea nitrogen increase. Unfortunately, the excretion of urea was not estimated.

Uric Acid.—The relationship between the concentration of uric acid in the blood and the rate of excretion (mg. per hundred c.c. of blood divided by mg. per hour excreted) is of interest in considering the blood uric acid. It has frequently been demonstrated that uric acid is the most difficult of the nitrogenous waste products to eliminate, and that one of the first signs of failing kidney function is an increase of this substance in the blood.²³ Accepting 3 mg. per hundred c.c. of blood as being the normal upper limit, we find that in 67 per cent. of the first twenty-eight cases abnormally high blood uric acid was noted. In only 14 per cent. of these cases did we find a uric acid excretion index above 0.2 (Watanabe's figure of slightly impaired kidney function²⁴), and in many cases (Nos. 15, 17, 21 and 25) we found a very free excretion associated with a high concentration in the blood, pointing to an increased production of uric acid. As the diet was low in purins and none of these patients had a leukocytosis at the time of examination, one naturally thinks of liver nuclear substance as the source of this uric acid.

TABLE 3

Case	Urobilinogen	Urobilin	Combined Excretion	Relative Oxidation of Urobilinogen	Blood Cholesterol, per Cent.
Liver cases having bile pigment in plasma—9, 11, 19 to 21, 23 to 28.....	12.5	7.16	19.66	57	0.238
Improved liver cases, no bile pigment in plasma—2 to 8, 10, 12 to 18, 22....	5.34	3.26	8.6	61	0.224
Debilitated cases, not associated with disordered liver—29 to 34.....	4.92	5.68	10.6	115	0.156
Recovered cases, not associated with disordered liver—35 to 40.....	1.18	2.07	3.25	175	0.154

Effect of Exercise.—The deleterious effect of exercise on debilitated patients is well shown in Table 4. In the first group, constituting the more serious cases, the urea nitrogen is practically normal; so also the creatinin. There is a slight increase in blood uric acid, but the excretion is very good. These patients were confined to their wards. The second group is made up of patients who had apparently recovered. The diet of this group is 4 per cent. richer in protein, but the

23. Myers, V. C., Fine, M. S., and Lough, W. G.: Arch. Int. Med.: **17**:570 (May) 1916. Baumann, L., Hansmann, C. H., Davis, A. C., and Stevens, F. A.: Arch. Int. Med **24**:70 (July) 1919.

24. Watanabe, C. K.: Am. J. M. Sc. **154**:76, 1917.

blood analyses show 57 per cent. more urea nitrogen, 9.2 per cent. more uric acid, 37 per cent. more creatinin, and a little more than one-half the ability to excrete uric acid as shown by the index; these patients, being apparently well, were unrestrained. Reference will be made later to the association of glycogen in the liver with a protection of that organ against poisonous substances. It may be stated, however, that the susceptibility of the liver to the destructive action of circulating toxins is in inverse proportion to the amount of glycogen contained in that organ. Hammarsten and Hedin²⁵ point out the fact that, during rest, the glycogen content of the liver is greatly increased, and that it is diminished during work. In dogs, Külz found the liver glycogen reduced to a minimum after a period of a few hours hard work. Considering this with the results shown in Table 4, we see that in the debilitated patients the effect of exercise is to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins.

TABLE 4

Cases	Blood			Index of Uric Acid Excretion*	Protein in Diet		
	Uric Acid, Mg. per 100 C.c. of Blood	Urea N, Mg. per 100 C.c. of Blood	Creatinin, Mg. per 100 C.c. of Blood		Animal, Gm. per Day	Vegetable, Gm. per Day	Total, Gm. per Day
Liver cases, confined to hospital ward—6 to 10, 17 to 28.....	3.57	21.0	1.87	0.064	98	46	144
Liver cases; debilitated; unrestricted; up and about—1 to 5, 11 to 16.....	3.9	33.0	2.57	0.121	90	60	150
Debilitated cases, not associated with disordered liver; up and about—29 to 34.....	4.37	40.5	2.02	0.077	90	60	150
Recovered cases, not associated with disordered liver; up and about—35 to 40.....	3.05	18.5	2.1	0.086	91	59	150

* Milligrams per 100 C.c. of blood divided by milligrams per hour excreted.

In this type of poisoning, decreased oxidative activity has been held accountable for the free autolysis occurring in the liver.²⁶ Our figures indicate an increased oxidative activity during absolute rest and are a further plea for rest during the treatment of these patients.

A possible explanation of the "delay" in poisoning by *arsenobenzol*, *chloroform*, etc., presents itself. Harrison¹ suggests that each dose of *arsphenamin* contributes its quota of damage to the liver, and that a final dose precipitates the toxic symptoms. In many cases, however, the toxic symptoms do not appear for weeks after the last treatment. It seems quite possible that in these cases the damaged organs are

25. Hammarsten and Hedin: *Physiological Chemistry*, London and New York, 1915, p. 391.

26. Wells, H. G.: *J. A. M. A.* **46**:341 (Feb. 3) 1906.

able to functionate during the course of treatment, when dietetic and physical restrictions are imposed; but when these are removed, and the patient returns to work and an unrestricted diet, the straw "which breaks the camel's back" has been added and toxic symptoms appear. This is well illustrated in Case 19. The patient had received 4.05 gm. of novarsenobillon in seven weekly doses; during the treatment, and for the following three weeks, he remained in the hospital and had no toxic symptoms. He was given seven days leave, however, and returned toxic and jaundiced. Similar observations were made in the case of another patient (Case 8). Assurances were given by each of these men that their lives were abstemious during their absence.

Clinical Application.—From the above results it would seem that, in addition to considering the protein intake of these patients, we must carefully regulate their exercise. Physical examination fails us in classifying these cases, and resort must be had to some functional test if we are to avoid toxic symptoms. In Table 4 the index of uric acid excretion appears to be the best test, but the labor entailed tends to preclude it as a routine method. The estimation of the urea in the blood is the second choice, and its routine use in institutional treatment is quite practicable. An abnormally high value in a patient at rest would be an indication for reducing the protein in the diet, while similar results in "up patients" would, perhaps, call for both rest and protein restriction.

Diet in the Treatment of Syphilis.—Experimental toxic jaundice has added greatly to our knowledge of liver damage and repair. The lesions produced in the liver by arsenobenzol derivatives are similar to those produced by chloroform and phosphorus, being essentially a fatty infiltration, with more or less necrosis of the liver cells. Opie and Alford²⁷ have shown that in both chloroform and phosphorus poisoning, less damage is done to the liver if a carbohydrate diet is given. Graham²⁸ demonstrated that in dogs the resistance of the liver to chloroform is proportional to the amount of glycogen in that organ. Rettig²⁹ has made similar observations in connection with phosphorus poisoning.

Many interesting and practical observations, which might well be applied to the toxic cases under discussion, have been made by Davis and Whipple³⁰ from their experiments on liver destruction and repair in dogs poisoned by chloroform. Their findings may be summarized as follows: (1) In starvation, a maximal injury to the liver is to be

27. Opie, E. L., and Alford, L. B.: J. A. M. A. **62**:295 (Jan. 24) 1914.

28. Graham, E. A.: J. Exper. Med. **21**:185, 1915.

29. Rettig, H.: Arch. f. exp. Path. u. Pharmakol. **76**:345, 1914.

30. Davis, N. C., and Whipple, G. H.: Arch. Int. Med. **23**:612 (May) 1919.

expected. (2) Sugar and diets rich in carbohydrates, fed in the days preceding chloroform anesthesia, exert a marked protective action against liver injury. (3) Fats alone, or combinations of food containing fat in large proportion, induce a maximal susceptibility to liver injury. (4) Skim milk alone is highly protective. (5) A diet of bread and skim milk or any rich carbohydrate diet gives the optimum liver repair. (6) A diet of cooked skeletal muscle is not favorable for rapid liver repair. (7) Fat diets do not aid in liver repair.

Lusk³¹ has shown that, in phosphorus poisoning, when the body carbohydrates are lowered, protein metabolism is greatly increased. This is explained by Lüthje³² and Cathcart³³ who conclude that carbohydrates are necessary in the synthesis of protein from the absorbed products of protein digestion. A rich carbohydrate diet would, therefore, ensure a complete assimilation of the protein and call for but a minimum protein intake. In determining this minimum, many factors come into play; these have been considered carefully and applied by Chace and Rose³⁴ in their dietetic treatment of nephritis. These authors find that 60 gm. of mixed animal and vegetable protein is quite sufficient for patients under treatment, provided the necessary carbohydrate is given to make up their fuel requirements.

It would seem advisable in the treatment of syphilis to institute a rich carbohydrate diet very low in fat and protein. This diet should precede the treatment by several days and should be continued throughout its full course. The high blood urea and the prolonged convalescence in our reported cases emphasize the advisability of such a diet being used.

SUMMARY

A report is made on the chemical blood and urine analyses in twenty-five cases of toxic jaundice following combined arsenical and mercurial treatment for syphilis, on two cases of catarrhal jaundice, on one case of syphilitic hepatitis, and on twelve cases in which patients were recovering from illnesses not associated with the liver.

Arsenic tests were made on the morning urines at periods ranging from 24 to 157 days after the last treatment and none was found. The twenty-four-hour urines were normal, excepting for pathologic pigments in some of the cases.

Patients clinically jaundiced had bile pigment in their urine. Bilirubin estimations in the plasma, according to Blankenhorn's dilution method, compared favorably with Gmelin's tests and the clinical findings.

31. Lusk, Graham: *Am. J. Physiol.* **1**:5, 1898.

32. Lüthje, H.: *Arch. ges. Physiol.* **113**:547, 1906.

33. Cathcart, E. P.: *J. Physiol.* **39**:311, 1909.

34. Chace, A. F., and Rose, A. R.: *J. A. M. A.* **69**:440 (Aug. 11) 1917.

Of the liver cases, those patients with bilirubin in the plasma excreted more than twice as much urobilinogen as did those patients who were free from jaundice; the nonjaundiced liver patients excreted more than twice as much as the well persons. Of the cases not associated with disordered livers, the debilitated patients had more than twice the urobilinogen excretion of the well persons.

In the twenty-eight liver cases, the rate of excretion of urobilinogen was one third greater in the early morning than was the average rate during the day.

In the urines, the relative oxidation of urobilinogen to urobilin was greatest in the well persons, less in the debilitated persons; about one third as much in the nonjaundiced liver patients, and still less in the jaundiced liver patients. The relative oxidation was greater in the early morning than in the twenty-four-hours specimens.

The patients with toxic jaundice had a marked increase in blood cholesterol, the jaundiced patients (being also the severe cases) had the greatest increase. In the cases not associated with liver disturbance the cholesterol value was normal.

Sugar estimations in blood and urine revealed no disorder of carbohydrate metabolism.

Blood creatinin estimations showed no marked departure from the normal. Uric acid estimations in the blood and urine indicated an increased production of this substance.

The values for urea nitrogen are normal in the well persons. Of the remaining cases, some patients show normal values, but the majority are above normal. This seems to be due to the high protein diet and deficient physical restrictions placed on these men.

The effect of exercise on debilitated patients seems to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins. This, associated with an increase in the diet proteins, is given as an explanation of the "delay" in poisoning by arsenobenzol, chloroform, etc. Arguments are advanced for the adoption of a diet rich in carbohydrate and very low in fat and protein in the treatment of syphilis.

CONCLUSIONS

1. In patients whose livers are damaged by arsenobenzol derivatives, an increase of cholesterol in the blood is an early and marked sign; it persists after other clinical signs have disappeared; its routine estimation may be of value in detecting the onset of liver injury in patients under antisyphilitic treatment.

2. In debilitated patients, the oxidative activity of the urine is decreased. This decrease is much more marked if the liver is disordered. In such cases the oxidative activity is greatest during absolute rest.

3. Exercise should be restricted greatly during the course of anti-syphilitic treatment and for the following few weeks.

4. A diet, rich in carbohydrate and very low in fat and protein, should precede, accompany and succeed the administration of arseno-benzol derivatives in the treatment of syphilis.

5. Increase of protein in the diet, and of exercise, should be controlled by the estimation of the urea in the blood.

6. The appearance of toxic symptoms in delayed poisoning by arsenic, phosphorus, chloroform, etc., is possibly due to the premature increase of protein in the diet, and of exercise in these cases.

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