AUTOHEMAGGLUTININS AND HEMOLYSINS WITH HEMOGLOBINURIA AND ACUTE HEMOLYTIC ANEMIA, IN AN ILLNESS RESEMBLING INFECTIOUS MONONUCLEOSIS*

By Laurence B. Ellis, M.D., Oscar J. Wollenman, M.D., and Richard P. Stetson, M.D.

ACUTE acquired hemolytic anemia is uncommon, but dramatic in its clinical picture and often disastrous in its outcome. In 1940, Dameshek and Schwartz\(^1\) assembled about 100 cases reported in the literature since 1907, in which no definite etiology was evident. In addition, as cited by these authors, cases have been reported in which the anemia developed in association with definite or probable etiologic factors. These include malaria, infections with streptococci, staphylococci and certain anaerobic organisms, as well as tuberculosis, syphilis and ankylostomiasis; also pregnancy, lymphoma, leukemia, carcinomatosis; and, finally, various drugs, especially the sulfonamides but also arsenical preparations, phenylhydrazine and acetanilide. Hemolytic anemia has also been reported in association with atypical pneumonia of unknown etiology\(^2,3\) and its occurrence in patients who have received sulfonamides is well established.\(^4\) Studies of these cases in regard to the presence of hemagglutinins and hemolysins have given varied results.

The case of acute hemolytic anemia with hemoglobinuria which is herewith reported is of interest because of the association of the unusual combination of autohemagglutinins and hemolysins occurring in the presence of morphologic changes in the white blood cells and heterophile agglutinins in the blood serum consistent with infectious mononucleosis, together with a positive Donath-Landsteiner reaction and the absence of evidence of syphilis.

The patient was observed during the acute stage of his illness by two of the authors (O. J. W. and L. B. E.) and more than two years later by the third author (R. P. S.).

REPORT OF CASE

Present Illness: H. J. H., a 21 year old single white male was admitted to an Army hospital in the European Theater on January 9, 1945, with a three day history of "bloody urine." Two weeks prior to admission he had developed an upper respiratory tract infection with a nonproductive hacking cough, headache, moderate nausea and anorexia. There was no vomiting until the day before admission when he had vomited once without hematemesis. On the evening of January 6, he first noted dark "bloody" urine, unaccompanied by urgency, frequency, dysuria or nocturia. The dark urine continued for the three days prior to admission. During this interval he developed a steady aching pain in the epigastrium and in the lumbar region. Generalized weakness and dyspnea on exertion became moderately distressing, but he continued on duty until admission. At no time did he experience chills, fever, icterus, or symptoms referable to the lower intestinal tract. His weight had decreased from his usual 128 pounds to 105 pounds on admission.

From the Thorneike Memorial Laboratory and the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

* This patient was observed from January to March, 1945, in an Army Hospital in the European Theater of Operations and subsequently in 1947 in a Veterans' Administration Hospital.
Past History: In 1937 he had an uncomplicated appendectomy; in 1941, a hemorrhoidectomy. On July 21, 1944 he was admitted to an Army General Hospital with lymphadenitis of the right arm and was discharged well on August 10. On August 24, 1944 he developed impetigo and was treated with ammoniated mercury and ultra violet light until September 16, 1944 when he was discharged as well. From September until the present illness, approximately four months later, he enjoyed good health. In November, 1944 his attention had first been called to asymptomatic enlargement of his finger tips which had not changed since, to his knowledge.

During the few days immediately preceding entry, he had developed a generalized pruritic skin lesion which, on admission, proved to be scabies. During his three years of army service he had never had tropical service; and he had not been exposed to any known hemolytic agents. He had received no sulfonamide drugs for at least six months prior to his illness. His diet had been adequate. Alcohol had not been used habitually nor in excess immediately prior to the present illness. There was no history of venereal disease. He had never experienced an illness similar to the present malady, nor had he ever been seriously ill.

Family History: No similar illness was known. The familial history was noncontributory.

Physical Examination: Temperature 99.4 F., pulse 110, respiration 20, blood pressure 120 mm. of mercury systolic and 70 mm. diastolic. He was ambulatory and complained chiefly of weakness. He did not appear acutely ill but was pale and slightly icteric. Scabetic furrows and scratches were present over the trunk and extremities. (Subsequent treatment for scabies led to rapid clearing.) The mucous membranes were moderately pale but presented no evidence of hemorrhage or ulceration. There was a nontender left infra-auricular lymph node approximately 1 cm. in diameter. No other lymphadenopathy was detected. The thyroid was not enlarged. The chest was symmetrical and the examination of the lungs was normal. The heart was not enlarged. There was a strong apical impulse and a blowing apical systolic murmur was heard on auscultation. The abdomen was scaphoid with an indefinite epigastric tenderness. The liver and spleen were palpable only on inspiration and were tender. The kidneys could be palpated but were not enlarged or tender. The genitalia were normal. The fingers presented a striking terminal enlargement characteristic of clubbing; the nails appeared otherwise normal. The toes did not show similar changes. The extremities were not cold or sweaty. Examination of the long bones, skull, the muscular and the neurologic systems was not remarkable. There was no demonstrable edema or evidence of dehydration.

LABORATORY DATA

Methods Employed: References are given below to the technical methods employed in the laboratory examinations.

Urine Examination: hemosiderin (Rouss technic); porphyrins; alkapton bodies; bile (Rosenbach's modification of Gmelin's test); urobilinogen (Wallace and Diamond modification of Ehrlich aldehyde test); hemoglobin in plasma and urine; indican (Obermayer's test).

Blood Examination: hemoglobin (alkaline hematin method using a Coleman spectrophotometer); red cell fragility; erythrocyte count; platelet count; bleeding time (Duke's method); clotting time; hematocrit and sedimentation rate (Wintrobe method); test for sickle cell trait.

Serologic Examination: heterophile agglutination, presumptive test (Davidsohn technic); Donath-Landsteiner; hemolysis test with acidified serum; cold hemagglutinins.

Other methods employed were either too well known to require comment or are described in the text.

Hematologic data during this hospitalization are given in table 1 and figure 1.

RESULTS

1. Anemia. The anemia was obviously hemolytic in type as evidenced by extreme hemoglobinuria, and became profound on the day following admission, the hemoglobin dropping from 12.2 grams per cent at 10:00 A.M. to 5.9 grams per cent by 3:00 P.M. of the same day. At this time blood platelets were 232,000; bleeding time one minute; clotting time five and one-half minutes (capillary tube), and clot re-
Table I

| Date | Hct | RBC | WBC | Differential | Hema-
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</table>

*1:64 Patient's cells.

NPN 18 mg. %, Bl. Sugar 112 mg. %, lymphocytes atypical Acid hemolysis and sickling neg., Donath-Landsteiner positive Blood Kahn and Wassermann neg.

Fragility of RBC normal

Sed. of RBC 1 mm./min.

Total prot. 9.1 Gm. %, alb. 5.8, glob. 3.3

Fragility of RBC normal

BMN +22

Donath-Landsteiner pos., MCV 92, MCH 31, MCHC, x8

See Tests—Tables 4 and 5

Donath-Landsteiner neg.
tension normal. The osmotic fragility test of the patient's red blood cells was identical with the control on the second hospital day, on three subsequent occasions within the next month, and two years later, in 1947. During the first two days difficulty was encountered in performing erythrocyte counts due to clumping of the cells in the pipet at the room temperature of approximately 20 degrees Centi-

![Graph](https://via.placeholder.com/150)

**Fig. 1**

grade. Subsequently warm saline solution was employed as a diluent and counts were then satisfactorily made.

The course of the anemia is shown in figure 1. Therapy consisted of transfusions of whole blood and concentrated red cells as described below, iron therapy and a high caloric, high vitamin diet.

2. **Morphology of the Blood.** Examination of the morphology of the erythrocytes was not striking. The anemia was essentially normocytic and normochromic and the red blood cells appeared morphologically normal. No nucleated red cells were
observed. The reticulocytes rose during the first and second week as shown in figure 1. There was an initial leukocytosis on January 10 of 24,300, with a differential of segmented polynuclear cells 32 per cent; eosinophiles 2 per cent; lymphocytes 64 per cent; monocytes 1 per cent. The lymphocytes were typical of the cells seen in infectious mononucleosis: the majority conformed to Downey's Class I, a small percentage were Class II and III. The leukocyte count did not exceed 10,000 per cubic millimeter after the second week and the relative lymphocytosis with the atypical lymphocytes gradually disappeared.

3. Hemagglutinins and Hemolysins. On admission hemagglutinins in the patient's serum with red cells of blood group O were demonstrated in a dilution of 1:256 at 4-6 degrees Centigrade. Clumping also occurred at 10 and 20 C and persisted when the test was carried out in the incubator at 37 C. When preparations which previously had been chilled at 4-6 C were subjected to a temperature of 37.5 C for one hour the clumping persisted and hemolysis occurred. There was no hemolysis at 4-6 C. After subjecting the patient's serum to a temperature of 56 C for inactivation of serum complement hemolysis was not observed but agglutination reactions were maintained. The hemagglutination against red cells of blood group O dropped to 1:64 by January 14, where it remained throughout this hospital admission.

The presumptive (table 2) and more complete Donath-Landsteiner tests (table 3) were strongly positive on admission; guinea pig serum was not available for addition as a source of complement to the heat inactivated serum. Donath-Landsteiner tests were repeated seven weeks later, with the same positive result. The Kahn and Wassermann tests were negative on four occasions during this month, and again in December, 1945 and January, 1947, and there was no history or physical sign of syphilis.

The relationship between chilling of the patient and the development of increased hemoglobinemia and hemoglobinuria was explored but unfortunately without conclusive results. During his hospitalization the patient was exposed to the usual environment of a drafty Nissen hut ward heated by coke stoves in England in the winter. During the first day of his stay he was a "bed patient," but was rather recalcitrant and difficult to keep in bed. The opportunity for chilling undoubtedly existed. No hemoglobinuria was present after the fourth hospital day. Obvious hemoglobinemia was observed on admission and on several occasions during the
first four days of hospitalization. Subsequent observations of the plasma showed moderate hemoglobinemia, above the level of controls, until January 16. Quantitative results are not reported because of difficulty in preparing a proper benzidine reagent. An attempt was made to test the effect of chilling by placing the patient's arm in ice water on March 13. The experiment had to be terminated in fifteen minutes because the patient fainted. No hemoglobinuria developed and the changes in the red blood cell count and level of free plasma hemoglobin were equivocal (table 4). The high levels for plasma hemoglobin in all control samples were considered to result from the benzidine reagent as mentioned above; precautions were taken to prevent hemolysis in obtaining the blood samples.

As shown in table 5, the hemolysin was absorbed from the patient's serum at 4-6 C. by normal group A red blood corpuscles and was not removed by three washings.
in saline at room temperature. The hemolysin was active only in the presence of complement since inactivation of normal serum at 36°C prevented the hemolysis which occurred with fresh unheated serum.

4. Heterophile Antibody. On admission, the heterophile agglutination was positive in a dilution of 1:1024, and remained at that level 10 days after admission on January 19. On February 10 it had fallen to 1:128, at which level it persisted throughout his stay in this hospital. Unfortunately, it was not possible to absorb the serum with guinea pig kidney or ox cells to determine the variety of heterophile antibody.11

<table>
<thead>
<tr>
<th>Tube number</th>
<th>RBC—5% suspension in saline 0.5 cc.</th>
<th>Serum—fresh 0.5 cc.</th>
<th>Serum—heated 5 min. 36°C, 0.5 cc.</th>
<th>Treatment of mixtures</th>
<th>Hemolysis</th>
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<tr>
<td>1</td>
<td>C*</td>
<td>P*</td>
<td>Chilled 20 min. at 4°-6°C, incubated 1 hr. at 37.5°C</td>
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<tr>
<td>2</td>
<td>C</td>
<td>P</td>
<td>Chilled to 4°-6°C, centrifuged, serum and cells separated at 4°-6°C. = P₂ and C₂</td>
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<tr>
<td>3</td>
<td>P fresh</td>
<td>P₂</td>
<td>Chilled 10 min. at 4°-6°C, incubated 1 hr. at 37.5°C.</td>
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<td>4</td>
<td>C₂ (Washed 3 times in saline, 37°C)</td>
<td>C</td>
<td>Incubated 1 hr. at 37.5°C.</td>
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<td>5</td>
<td>C fresh</td>
<td>P₂</td>
<td>Chilled 10 min. at 4°-6°C, incubated 1 hr. at 37.5°C.</td>
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<tr>
<td>6</td>
<td>C₂ (Washed 3 times in saline)</td>
<td>C</td>
<td>Incubated 1 hr. at 37.5°C.</td>
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</table>

*P = Patient; C = Normal Control; red cells washed three times in physiological saline at room temperature. Both blood samples were Group A.

5. Blood Grouping and Transfusion Therapy. Upon admission blood grouping with rabbit immune sera and washed red cells of the patient at 37°C indicated that the patient belonged to blood group "O." The same group was recorded on his Army Identification tag. Later, it was demonstrated both by us and the North East London Blood Supply Depot that the patient was, in reality, blood group A, as demonstrated by high titer grouping serums. No studies were made to determine the possible subgroups A₁ and A₂.

In spite of hemagglutination demonstrated at room temperature and at 4°-6°C, it was evident that transfusions were necessary to combat the rapid fall of the hemoglobin. Since the initial blood group was considered to be group O, 1500 cc. of group O blood, warmed to body temperature, was given on the evening of
January 10. There was no reaction. The Rh blood group could not be determined at
this time since anti-Rh serum was not available.

Transfusions were continued and a total of 7500 cubic centimeters of blood was
given between January 10 and 21.* The patient occasionally complained of pain in
the right and left upper quadrants following transfusion but no evidence of in-
creased hemolysis could be demonstrated as having occurred. Only group O blood
without Rh determination had been given up until January 24. At that time anti-
Rh serum became available and a mixture of Rh negative and positive cells was
demonstrated in the patient's blood. Rather than speculate which were the
patient's cells and which the donor's, in view of the 7500 cubic centimeters of
undetermined Rh blood which had been given, concentrated Rh negative group A
cells from 2000 cc. of whole blood were suspended in physiologic salt solution and
administered at room temperature on January 24. A transient slight pyrogenic re-
action followed. No further transfusions were given prior to evacuation to the
United States.

6. Urinary Findings. The admission urine specimen, January 9, was port wine in
color, showed 3 plus albumin, a 4 plus reaction for hemoglobin and a 1 plus bile
test. Tests for sugar, acetone, porphyrin, indican, alkapton and hemosiderin were
negative. Urobilinogen and urobilin were not determined on this specimen. Num-
erosus granular casts were present in the centrifuged specimens but no white blood
cells, red blood cells or blood cell casts. On the second hospital day the urine was
dark but not red. It contained a 2 plus albumin, 2 plus bile, but the test for hemo-
globin was negative and the sediment was negative. Spectroscopic examination of
the specimen by the North East London Blood Supply Depot, Luton, England,
showed an increase in urobilinogen, urobilin and bile but no evidence of porphy-
rins. On the fourth hospital day the morning specimen showed a 4 plus reaction to
benzidine, an afternoon specimen was free of hemoglobin and no specimen there-
after contained either hemoglobin or bile. Urine urobilinogen was positive in 1:40
dilution on the fifth and eighth hospital days and remained positive in 1:80 to
1:160 dilution until January 24 when it became entirely normal. Concentration
tests and fractional phenosulphonphthalein excretion tests were normal.

7. Miscellaneous Tests. In addition to the laboratory examinations already dis-
cussed, numerous other tests were carried out and are shown in table 1. All, in-
cluding chest roentgenograms on admission, were normal or unrevealing as to the
nature of the hemolytic process.

Course in Hospital. During the first two weeks the patient was critically ill, but
throughout this period, as well as later, was active and loathe to stay in bed. By
January 22, the anemia had ceased to progress and from then on steady improve-
ment occurred. A peak reticulocytosis of 9.8 per cent was found on February 10.
During the period of marked anemia the patient exhibited a low-grade fever, reach-
ing 101 F. on two occasions. As the red blood cell level was restored, the tempera-
ture returned to normal and after February 8 never exceeded 99. Fluid intake and
output were satisfactory. The patient gained 5 pounds during the two months' 
hospitalization.

* All blood was generously supplied by the N. E. London Blood Supply Depot, Luton, England.
Subsequent Course and Present Condition. The patient was evacuated to a hospital in the United States as an ambulatory patient on March 12, 1945. There, in April, the heterophile test was still positive (titer unavailable) and serum phosphorus, calcium and alkaline phosphatase determinations were normal, as was an electrocardiogram. Roentgenograms showed widespread slight osteoporosis of the tibiae, fibulae, lumbar vertebrae and skull. Biopsy of a lymph node from the right inguinal region was reported as showing "subacute inflammation, not inconsistent with infectious mononucleosis." He was transferred to another hospital in December, 1945 when he developed a fissure of the rectum and hemorrhoids and was operated upon uneventfully. At this time, the sedimentation rate was 32 millimeters per hour; whole blood chlorides 479 milligrams per cent; CO₂ combining power 61 volumes per cent; serum phosphorus 1.8 milligrams per cent; serum calcium 11.3 milligrams per cent; and urea clearance test was 72 per cent of normal. Sternal puncture was negative and a "modified" Donath-Landsteiner test was now negative. During this entire period he remained weak, underweight, developed pains in his legs of increasing severity; clubbing of the toes was observed at that time with an apparent increase in the clubbing of the fingers. He was discharged from the Army in January, 1946.

On January 21, 1947, he entered a Veterans' Administration Hospital for further study, where he remained until March 7. His complaints were persistent aching in the legs, a pressure sense in the rectum with frequent mucoid defecations, listlessness, nervousness and chronic fatigue. On physical examination he appeared somewhat agitated; there was audible hyperperistalsis and tenderness upon palpation of the rectum and prostate; clubbing of the fingers and toes; cold, clammy hands and feet, and "marked" adenopathy in the inguinal, femoral and posterior cervical regions.

Extensive laboratory studies were made at this time.* They are shown in table 1. In essence, all hematologic studies were then within normal limits. Six serologic tests for syphilis were carried out and were negative (Kahn, Kolmer, Kline, Eagle, Hinton, Mazzini). Stool examination showed mucus but no blood, parasites or ova. Sigmoidoscopy was normal.

Roentgenograms of the chest including bronchograms were normal. The hands and feet and long bones showed clubbing of the terminal phalanges of all fingers and toes; and there was expansion of the carpal and metacarpal bones with coarseness and trabeculations and thickening of the cortex. The skull had a somewhat granular appearance. A barium enema revealed a spastic colon.

Discussion

Did this patient have infectious mononucleosis? The heterophile antibody decreased coincident with the decrease in serum hemagglutinins but at all times it was positive in much higher dilution than was the hemagglutinin. Belk, in studying a patient convalescent from infectious mononucleosis, found not only heterophile agglutinins and hemolysins against sheep, horse, rabbit and pig cells, but also autoagglutinins which were active below 10 Centigrade, but not at 37. He suggested that a nonspecific stimulus in this disease might result in a widespread production of antibodies. In a study of cold agglutinins, Favour found them present in four of ten cases of infectious mononucleosis, with a maximum titer of 1:180. Springyarn et al. have demonstrated them in seven cases of this disease. In their search for cold hemagglutinins in various disease states, Finland and his associates found none in the three cases of infectious mononucleosis which they investigated. Davidsohn found the titer of isoagglutinins normal in 44 cases of infectious mononucleosis.

The morphologic white blood cell picture of hemolytic anemia is usually described as an absolute and relative polymorphonuclear leukocytosis. An absolute and relative lymphocytosis, as seen in our patient, is unusual, and the presence of atypical lymphocytes, characteristic of those found in infectious mononucleosis is

* Many of the tests were generously made by the Blood Laboratory of the Pratt Diagnostic Hospital, Boston.
even more unusual. Dameshek\textsuperscript{4} has reported an instance of hemolytic anemia in a patient with infectious mononucleosis who had also received sulfadiazine. A potent iso- and autohemagglutinin especially active at ice box and room temperatures was present in the serum. He felt that the drug played an important role in the production of the anemia. With this exception, no instances of hemolytic anemia occurring in infectious mononucleosis have come to our attention. In their review of hemolytic anemias Dameshek and Schwartz\textsuperscript{1} cited none. In his monograph on infectious mononucleosis Bernstein\textsuperscript{8} stated that "anemia of any appreciable degree does not appear unless associated with some complicating feature such as hemorrhage of dietary deficiency."\textsuperscript{11}

The evidence in this case suggests the possible diagnosis of infectious mononucleosis although it cannot be proved. It was not possible to classify the heterophile antibody by absorption studies.\textsuperscript{11} Although there was a history of an upper respiratory infection two weeks before the first hospital admission, there was insufficient evidence to establish a diagnosis of atypical virus pneumonia. Since no other etiologic factor for his hemolytic anemia was evident, a causal connection between his anemia and the development of abnormal serum antibodies is suggested, possibly related to a disease resembling infectious mononucleosis.

Another feature of interest is the positive Donath-Landsteiner reaction. Such reactions usually have been found in cases of paroxysmal hemoglobinuria associated with syphilis,\textsuperscript{9} although a few instances of its occurrence in hemolytic syndromes in the absence of syphilis have been reported. In our patient there was no evidence of syphilis. Stats and Wasserman,\textsuperscript{19} who estimated that 92. per cent of cases showing a positive Donath-Landsteiner reaction have an associated syphilis, were of the opinion that fundamentally different antibodies are responsible for cold hemagglutinins and a positive Donath-Landsteiner reaction. They found but one case in the literature in which both have been reported\textsuperscript{19} and refer to one further case with a positive Donath-Landsteiner reaction in which cold hemagglutination at from 0 to 3 Centigrade was observed.\textsuperscript{21}

A relationship between the clubbing of the digits and the blood changes is unlikely. The presence of cold hemagglutinins and the occurrence of hemolytic manifestations have been described in patients with peripheral vascular disease, especially of the vasospastic type such as Raynaud’s disease.\textsuperscript{19} Peripheral osteoarthropathy is generally considered to be related to abnormal circulation to the bone, but the association of clubbing with peripheral vascular disease is rare. In the present instance the clubbing preceded the acute hemolytic crisis and progressed after the hematologic abnormalities had disappeared and the hemagglutinins had diminished to a very low titer. This patient showed no evidence of peripheral vascular disease other than a tendency toward moderately cold and cyanotic hands and feet, with hyperhidrosis of the palms developing after his acute hemolytic episode. It is hardly tenable to relate the association of the bone changes to the hemolytic anemia or an illness resembling infectious mononucleosis unless the hypothesis is advanced that there was an underlying circulatory dystrophy with a chronic but minimal production of hemagglutinins which gave rise to a hemolytic crisis when the concentration of these antibodies was increased by the acute disease process.
SUMMARY AND CONCLUSIONS

A case is reported of a young man with acute hemolytic anemia and hemoglobinuria who presented an initial blood picture consistent with infectious mononucleosis, associated with a heterophile agglutination test positive in high dilution; auto-hemagglutinins, active in the cold, at room temperature and at 37 Centigrade; a hemolysin active at 37 C. after chilling, requiring the presence of a thermolabile component of serum for hemolysis; a positive Donath-Landsteiner test but no evidence of syphilis. In addition there was clubbing of the digits with certain other roentgenologic changes in the bones; absence of any other etiologic factors known to be concerned with such anemia; uneventful improvement under massive transfusion therapy, with apparent recovery from his hematologic disorder when studied two years later.

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REFERENCES

UNUSUAL PICTURE IN POSSIBLE INFECTIOUS MONONUCLEOSIS

AUTOHEMAGGLUTININS AND HEMOLYSINS WITH HEMOGLOBINURIA AND ACUTE HEMOLYTIC ANEMIA, IN AN ILLNESS RESEMBLING INFECTIOUS MONONUCLEOSIS

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