limb are, when possible, the best treatment for the paralysed muscles, and prevent the development of painful stiffness and various forms of neurotic hesitation in using the limb. In high median lesions passive flexion of the index finger is especially important to avoid stiffness of this finger in extension. In wounds of the brachial plexus the use of a sling and a soft pad in the axilla, if the deltoid is paralysed, combined with regular movements, is all the treatment of the resulting paralysis required during the first two or three weeks until the case reaches a special centre.

Lower Extremity.—The early treatment of injuries to the nerves of the lower extremity consists simply in maintaining, if possible, the range of movement of the joints. The only support likely to be required is for drop-foot, and, unlike that of the upper extremity, this palsy should be supported as soon as possible. A cradle should be used to relieve the pressure of bed-clothes and to allow movement of the limb. If the sole of the foot is anaesthetic it must be protected from injury, and when there is sufficient recovery to allow walking it is important to provide only well-fitting light boots without irregularities of the sole. The patient should be told of this need to protect anaesthetic skin from both injury and burns.

Finally, as with all traumatic war surgery, it must be stressed that attention to the morale of the patient is most important. As the medical officer has little time to give individual attention to cases of nerve injury, much depends on the massage department. The well-handled man is obviously keen to overcome his disability as much as possible. He moves the joints with vigour and confidence, and maintains the maximum use of his injured limb.

Summary

Quick neurological methods of examining wounded limbs for nerve injury, suitable for use by surgeons in a forward battle area, are described and illustrated.

Simple methods of recording are given.

In early treatment the dangers of splinting the fingers are emphasized. Early active or passive movement is valuable. Continual full relaxation of paralysed muscles is harmful.

Our thanks are due to Col. R. A. Broderick, D.S.O., M.C., for permission to refer to cases in No. 27 General Hospital.

ACUTE HAEMOLYTIC ANAEMIA

REPORT OF A CASE PRESENTING HITHERTO UNREPORTED FEATURES

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The purpose of this paper is to record a case of acute haemolytic anaemia occurring in a male adult, showing the rare phenomenon of auto-agglutination* and the possible presence of both an autohaemolysin and an autohaemolysinogen.

The Literature

It is outside the scope of this communication to review the whole of the literature relevant to this rare type of anaemia—a task which has been recently completed by Dameshek and Schwartz. Nevertheless a brief summary of the growth of our knowledge of this syndrome would appear to be a satisfactory point of departure.

Credit for the recognition of haemolytic jaundice as an entity apart from liver or bile-duct disease must be given to Hayem (1898) and Minkowski (1900). No further progress was made until 1907, when Chauffard demonstrated that in cases of chronic

* **Autohaemolysin:**—A haemolysin which is capable of acting against the blood corpuscles of the animal in whose serum it circulates. **Auto-agglutinin:**—An agglutinin which is capable of agglutinating the blood corpuscles of the animal in whose serum it circulates. **Isohaemolysin:**—A haemolysin capable of acting against the blood corpuscles of an animal of the same species. **Iso-agglutinin:**—An agglutinin in the blood serum of an individual which is capable of agglutinating the blood corpuscles of another animal of the same species. In humans these include the agglutinins which correspond to the well-known agglutinogens: A, B, and the Rh factor. (These definitions are in accordance with Ehrlich's lateral-chain theory.)

hereditary acholuric icterus with splenomegaly the erythrocytes were abnormally fragile in hypotonic solution. Between 1907 and 1914 several authors—e.g., Widal, Abrami, and Brulé—described a type of acholuric jaundice without a hereditary factor and occurring either alone or in the course of various diseases. These cases they called “acquired haemolytic icterus.” About the same time Chauffard, Troisier, and Vincent (1908) described a third type of case differing from the other two in that an iso-haemolysin was present in the serum of their patients during the height of the disease: these cases they called “haemolysin icterus.” Cases of these three types were then subdivided according as to whether they ran an acute, subacute, or chronic course. It is interesting, in view of the case herein reported, to note that in 1912 Roth described a case of haemolytic icterus in which the blood serum contained an auto-agglutinin and an auto-haemolysin. He put forward the view that “haemolysin icterus” was an unjustifiable term, and claimed that the haemolysis was the result of an abnormality of the circulating erythrocytes. Wide controversy now raged, and gradually the existence of an acquired type of haemolytic icterus was gravely doubted.

Interest in the condition was then apparently lost until 1925, when Lederer “discovered” his acute haemolytic anaemia. In spite of the fact that his cases were identical with many previously reported, they were accepted as examples of a “new” disease. His paper made no mention of iso-haemolysins or auto-agglutinins; indeed, these phenomena seem to have remained forgotten until Davidson's paper in 1932.

It is a matter of no small difficulty to discover how many cases of acute haemolytic anaemia have been reported, the chief difficulty lying in the fact that these cases have been described under many titles—e.g., “atypical anaemia,” “atypical pernicious anaemia,” “acute pernicious anaemia,” and so on. Again, many of the cases described as “acute” have a history which might be regarded as indicative of an exacerbation of a subacute or chronic disease. Dameshek and Schwartz, in their excellent review (1940), list 107 cases which they consider are entitled to the term “acute haemolytic anaemia.” I am convinced that, even here, considerable leniency has been shown by the compilers.

The aetiology of many haemolytic anaemias is well known—e.g., bacteria (streptococci), protozoa (malaria), and chemicals (phenylhydrazine). In the majority of cases, however, the cause is unknown; but, broadly speaking, two schools of thought have grown up, thus: (1) that the haemolysis is due to the presence in the serum or tissues of a haemolysin for the patient's own erythrocytes—i.e., an autohaemolysin; (2) that the haemolysis is the result of normal wear and tear, in the circulation, on abnormal (exceedingly fragile) erythrocytes. Present opinion favours Hypothesis 1, and this would appear to be justified by the nature of the marrow reaction alone, since it is unlikely that a marrow which is injured or deficient could respond so well to the demands made of it by the anaemia.

Iso- and Auto-haemolysins

Isohaemolysins were first demonstrated in a haemolytic state in paroxysmal haemoglobinuria. Here the haemolysin was shown by Donath and Landsteiner (1905) to be activated by cold and to act subsequently at room temperature. Their presence was later demonstrated in several cases of acute haemolytic anaemia by a number of investigators. Dameshek pointed out that although free circulating haemolysins could not be found in every case, that did not rule out their possible presence within the body tissues, and Troisier (1910) and Lieberman and Fenyvessy (1911) offered the explanation that a haemolytic amboceptor became fixed to the erythrocytes, which were thus rendered sensitive to the addition of complement.

While the discovery of iso-haemolysins is indicative of the possible or even probable aetiology of the disease, it cannot have such significance as the discovery of autohaemolysins; these, however, have rarely been demonstrable, and then only under abnormal conditions—e.g., at ice-box temperature. The existence of iso-haemolysinogens has not been reported.

Auto-agglutinins

Widal and many other early investigators commented on the concurrence of auto-agglutination in cases of acute acquired

haemolytic jaundice. They even claimed that this phenomenon was constant in these cases and of diagnostic value. These observations, like those of isohaemolysins, were quickly forgotten, and remained so until rediscovered by Giordano and Blum in 1937. Altogether about 8 cases showing auto-agglutination have been described, but it should be noted that it was rarely searched for in the other reported cases.

That there is a close relationship between iso-agglutinins and isohaemolysins has long been recognized. The relationship is, unfortunately, too close for easy investigation, for if the agglutinin titre of a serum is high the agglutination which occurs is so dense as to make haemolysis impossible, or at least difficult, even when the isohaemolysin titre is high. All attempts at differential precipitation of the two factors have so far failed.

The most recent contribution to our knowledge of haemolytic anaemia and its aetiology has been made by Dameshek and Schwartz. They gave graduated doses of guinea-pig erythrocytes to rabbits and thus obtained from the recipient animals a heterophilic haemolytic serum (for guinea-pig corpuscles). They then administered this serum to healthy guinea-pigs and, by varying the amount given, were able to produce various types of haemolytic syndrome, thus:

1. Large dose .. Fulminating haemolytic anaemia with haemoglobinuria
2. Moderate dose .. Acute haemolytic icterus (or anaemia)
3. Small dose .. Subacute haemolytic anaemia

They also observed that any of the various types of blood picture obtained in clinical cases could be produced in the same way, thus:

1. Spherocytosis
2. Increased erythrocyte fragility
3. Reticulocytosis
4. Pseudomacrocytosis, etc.

They deduced that, in view of the close resemblance of the experimental and the clinical anaemias, the various syndromes occurring in the latter were chiefly due to the amount of haemolysin present.

Case Report

The patient was a man aged 37, married, and employed as an engineer. His previous health was excellent. Inquiry into his family history produced no relevant data.

At 7 p.m. on Oct. 31 he suddenly and without warning felt faint while walking to his work. He had seemed perfectly well until that moment, and thought that the faintness would pass off. After a few steps he was forced to sit down by the roadside, and there recovered a little. Immediately he got up again he collapsed and lost consciousness. On regaining consciousness he attracted the attention of a passer-by and was assisted home. His doctor, on being summoned, noticed that the patient was jaundiced. Next day the jaundice was deeper and he had haemoglobinuria, but the stools were normal. When seen by his doctor on Nov. 2 the patient was still more deeply jaundiced, very ill, and disorientated. He was then sent into hospital. On admission he was very confused; temperature 102° F., pulse 114, respirations 22. His skin and mucous membranes were lemon-yellow, but, in addition to the jaundice, pallor was striking. Physical examination revealed no abnormalities other than extreme weakness, a thready pulse, and a tender spleen just palpable beneath the costal margin. The urine contained haemoglobin and a large amount of haemoglobinous deposit. No bilirubin was present—i.e., acholuric jaundice.

Blood.—Hb, 15%; R.B.C., 900,000; W.B.C., 25,000; platelets, 300,000; M.C.V., 90 c.u.; icteric index, 34; W.R., negative; Hess's test, negative; Ehrlich-Morgenroth test, negative. Blood film showed many normoblasts, some erythroblasts, marked immaturity of the granulocytes, and a few myelocytes and premyelocytes. Microspherocytosis was obvious. A noteworthy feature was the presence of degenerative cytoplasmic granules within 80 to 90% of the granulocytes.

Sternal Marrow.—Marked hypercellularity. Reaction predominantly erythroblastic, with many normoblasts and reticulocytes. Slight increase in myelocyte and premyelocyte numbers.

Serum Haemagglutinins and Haemolysins.—The appearance of auto-agglutination made typing for transfusion purposes difficult—i.e., the patient's serum agglutinated his own corpuscles at room temperature. This difficulty was overcome in two ways:

1. Since the auto-agglutinin was independent of the ordinary iso-agglutinins the patient's serum could be tested against group A and group B corpuscles. This was done, and both were agglutinated, suggesting that either the serum was from a group O patient or it had "panagglutinating" properties. Tested against normal group O

corpuscles, no agglutination took place, showing that the former hypothesis was correct.

2. The blood for typing was received into citrate solution at body temperature. The agglutination tests were made on warm slides, and thus the auto-agglutinin, which acts at temperatures below that of the body, was kept inactive. In this way the patient's cells were found to contain neither A nor B agglutinin.

The haemolytic properties of the patient's serum were next investigated, thus:

Test	Agglutination	Haemolysis (after 2 hours)
1. Ps + Pc	++	—
2. Ps + Ac	++	—
3. Ps + Bc	++	—
4. Ps + Oc	++	—
5. Ps (heated to 60° C.) + Pc	++	—
6. Ps (heated to 60° C.) + Pc + C	++	—
7. Ps + Oc + X	++	Unknown
8. Rs + Rc	++	—
9. Rs + Pc	++	—
10. Ps + Rc	++	—
11. Rs + Rc + X	++	Unknown

P = Patient during illness. R = Patient after recovery. A = Group A. B = Group B. O = Group O. s = Serum. c = Cells. X = Cellular fraction obtained by washing and crushing "P" cells.

Deductions

1. Granted that the patient is of group O, the agglutination of cells of groups A and B is clearly due to the presence in the patient's serum of the ordinary iso-agglutinins.

2. The auto-agglutination which is present at room temperature is due to an auto-agglutinin which acts in the absence of complement (see test 5 in Table).

3. The associated haemolysis requires the presence of complement, although the amboceptor itself is heat-stable (see test 6).

4. Sensitivity to the agglutinin can be transferred to normal group O cells by allowing them to stand in the filtrate of the patient's crushed, washed erythrocytes. Whether or not the cells are rendered sensitive to the haemolysin is not known, as obviously the prepared group O corpuscles are suspended in a haemoglobiniferous fluid (see test 7).

5. The phenomena of auto-agglutination and autohaemolysis disappear with recovery of the patient, and that this is due to an alteration in his corpuscles and not his serum is shown by tests 8 and 9.

6. The patient's corpuscles, after recovery, can be made sensitive to the auto-agglutinin once more by treating them as in deduction 4 above. Again, however, it cannot be stated whether or not haemolysis of the treated cells occurred.

7. The results demonstrate: (a) an auto-agglutinin, an auto-agglutinin, and an autohaemolysin; and suggest the presence of (b) an autohaemolysinogen.

Aetiology.—The results obtained by these investigations elucidate the mechanism but not the aetiology of the anaemia. The presence of degenerative granules within such a large number of the granulocytes is highly suggestive of a circulating toxin (Mendell *et al.*, 1936)—not necessarily of bacterial origin.

Treatment.—One pint of whole citrated group O blood was given on the fourth day after admission. A mild transfusion reaction occurred, but without any grave symptoms. From this time onwards the patient made an uninterrupted recovery.

Comment

I do not regard this as evidence of Lederer's reported dramatic response to one blood transfusion, since I am of the opinion that if the patient had not already begun to improve—haemoglobinuria had disappeared—at least the disease had limited itself by the time of transfusion. Further, it has frequently been shown that several transfusions are required in many of these cases, while in a few they prove altogether useless. In the latter group some cases have shown response to splenectomy, and this has led Dameshek and others to regard the spleen as the site of production of the haemolysin.

Summary

A brief survey of the growth of our knowledge of acute haemolytic anaemia is given.

The possible causes are discussed, especially the role of haemolysins.

A case of acute haemolytic anaemia is reported which showed auto-agglutination and autohaemolysis at room temperature.

The reactions of the patient's serum and cells during and after the disease are described.

The presence of a heat-stable auto-agglutinin and auto-haemolysin and an auto-agglutininogen is demonstrated.

The presence of an autohaemolysinogen is suggested.

Changes in the granulocytes are reported and their aetiological significance is indicated.

I wish to thank Dr. J. W. Macfarlane for permission to publish this report, and Dr. George Will, resident physician, for his help in the investigation of the case.

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TYPHUS FEVER IN GREAT BRITAIN

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Typhus fever is rare in this country, and in everyday practice is seldom considered in the differential diagnosis of pyrexia of uncertain origin. This might have unfortunate consequences at the present time when numbers of people are arriving here having travelled under conditions of war from districts where the disease is endemic or epidemic. The following report of a single case is therefore of topical interest and may serve as a useful reminder that typhus fever may make an unexpected appearance.

Case History

The patient, a man aged 24, was one of 19 men admitted to hospital on the evening of Jan. 5, 1944, from sick quarters on board ship. They had embarked on Dec. 20, 1943, from an area in which typhus was prevalent and all had been taken ill on the voyage. "Influenza" had been prevalent, and a number of the men, including the patient, had acute respiratory infections. The only available history of the case was as follows: Dec. 31: complained of headache, cough, and general muscular pains; temperature 102°. Jan. 1: progress satisfactory. Jan. 2: temperature, pulse, and respirations normal. Jan. 3: temperature 99°. Jan. 4: T. 101.2°; P. 80; R. 20. Diagnosis—bronchitis.

On admission the patient looked toxic and complained of severe headache, sore throat, and cough. He had a sharp rigor, and collapsed before being put to bed. On examination he was flushed; there were muco-pus in the nose and throat, definite bronchitis, slight general adenitis, and slight neck rigidity. There were healed scars of desert sores on both hands. No abnormality was found in any of the other systems. Temperature 103°; pulse 84; respirations 22. The subsequent course of events may be briefly summarized:

Jan. 6.—Temperature range, 100.4° to 103.4°; pulse 100; respirations 30. Patient flushed; conjunctivae injected; tongue dry and coated; non-adherent exudate on throat; slight adenitis; bronchitis less marked. Throat swab negative for *C. diphtheriae*, haemolytic streptococci, and Vincent's organisms. Leucocytes 12,800 per c.mm.—neutrophils 62%. No malaria parasites seen in film.

Jan. 7.—T. 102° to 103°; P. 110; R. 30 to 40. Patient drowsy, restless, and irritable; increased neck rigidity; respirations irregular; more intense bronchitis but no definite bronchopneumonia; moderate

albuminuria; hearing impaired; slight injection of both tympanic membranes.

Jan. 8.—T. 101° to 102°; P. 110; R. 40 to 50. General condition deteriorating; meningism; respiration of Cheyne-Stokes type; more definite evidence of bronchopneumonia. Urine: albuminuria, occasional granular casts. Blood: leucocytes 13,000 per c.mm.—neutrophils 90%. Cerebrospinal fluid: clear, pressure 220 mm. H₂O; protein 30 mg. per 100 ml., chlorides 690 mg. per 100 ml., sugar 65 mg. per 100 ml.; no organisms seen. Widal test—compatible with previous T.A.B. inoculation.

Jan. 9.—T. 99.4° to 105°; P. 120; R. 40 to 50. General condition unchanged. A sparse macular rash, comprising some 20 spots in all, on the flanks and anterior aspects of the shoulders was seen for the first time. The macules were 2 to 3 mm. in diameter, dusky red in colour, and did not entirely fade on pressure.

Jan. 10.—T. 101° to 102°; P. 120 to 130; R. 40 to 50. General condition and rash unchanged. More definite evidence of bronchopneumonia. Weil-Felix reaction reported positive.

Jan. 11–13.—T. 99° to 101°; P. 100 to 110; R. 40. Patient much quieter but still very drowsy; sleep disturbed by occupational dreams; appreciable loss of flesh.

Jan. 14–15.—T. 97° to 99°; P. 80 to 90; R. 30 to 40. Progressive improvement.

Jan. 17.—T. normal; P. 80; R. 20.

The subsequent course was uneventful apart from a voracious appetite.

Treatment was symptomatic except for 12 g. of sulphapyridine given between Jan. 7 and 9. Liberal amounts of bland fluids, glucose, and sodium chloride were given throughout the illness. Oxygen and cardiac stimulants were not required.

Weil-Felix Reactions.—Blood sera were examined on three occasions; the following titres were obtained:

Date	Type OX 19	Type OX 2	Type OX K
10/1/44	1 : 4,000	1 : 125	1 : 25
15/1/44	1 : 12,800	1 : 400	1 : 25
21/2/44	1 : 6,400	1 : 400	1 : 25

The maximal titre, 12,800 v. OX 19, thus occurred about the end of the second week of illness, as is usual in epidemic typhus. Five weeks later, when last estimated, this titre was 6,400. No significant reaction was obtained against *B. proteus* OX K. No antityphus vaccine has been given. *B. proteus* suspensions used were supplied by the Standards Laboratory (M.R.C.), Oxford, agglutinability being standard throughout.

Discussion

The incubation period of typhus fever is rarely less than 8 days; it is usually 8 to 13 days, but may be 20 days or even longer (Rogers and Megaw, 1942). Though infection might have occurred on board ship, it probably took place before embarkation on Dec. 20, either from a louse-bite or from infected formites. A third possible source was by droplet infection (Pole and Bensted, 1943). Presumably forms frustes and abortive and ambulant cases occur in typhus as in other fevers.

The rash appears on the fourth or fifth day. It was not seen in this case until Jan. 9, which suggests that the first day of the invasion period was Jan. 4 or 5. By this reckoning the earlier fever may have been due to a prodromal state (Harries and Mitman, 1940) or to "influenza," which, as stated above, was prevalent. On the other hand, the high-titre positive Weil-Felix reaction on Jan. 10 favours an onset as early as Dec. 31.

Diagnosis was rendered difficult by the reported normal temperature on Jan. 2, by the apparent delay in appearance of the rash and its scanty indefinite character, and by the absence of disproportionate tachycardia in the early stages. Other misleading features were the presence of membrane in the throat and the adenopathy. The decisive stages in reaching a correct diagnosis were: first, the recognition of typhus fever as a possible cause of the illness; secondly, the appearance of the rash; and, thirdly, the positive Weil-Felix test. The fact that the rash does not always appear renders the first of these all-important.

Precautionary measures taken in hospital included the shaving of the patient and the disinfection of his clothing and that of the other men from the same ship. Contacts were quarantined, and were inspected for lice on two occasions at an interval of seven days. No lice, bites, or scratches were found on the patient or on any of the contacts. Pathological specimens, especially blood, were carefully handled. In view of the possibility of droplet infection all attendants were masked and gowned. Typhus vaccine was not given to contacts or attendants in view of the time necessary to establish immunity and also because of possible undesirable effects if administered during the incubation period.

None of the other patients developed a positive Weil-Felix reaction. No secondary cases occurred locally or, so far as is known,