and of the State, and although it must be agreed that the care of rheumatic children deserves the first consideration, there is every justification to set up a system of cardiac clinics based on a nation-wide organization for the benefit of cardiac cases of any type.

The crippling effect of rheumatic heart disease, the growing incidence of arterial hypertensive

disease and of the degenerative cardio-vascular disease generally call for a comprehensive scheme providing up-to-date diagnostic and remedial facilities, as well as after-care and rehabilitation for all cases of cardio-vascular disease.

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HAEMOLYTIC ANAEMIA, WITH PARTICULAR REFERENCE TO CAUSE AND MECHANISM

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The anaemias resulting from abnormally rapid haemolysis constitute an important group of disorders of great interest to both clinician and pathologist, but although considerable progress towards their understanding has been made in recent years, much is still unexplained. In this short review general principles are first considered, then, choosing certain important types of haemolytic anaemia as examples, the various mechanisms of causation are discussed. Recent work of importance is mentioned as far as possible and some of the many points still requiring elucidation are indicated.

The Results of Increased Haemolysis

(a) *Increased blood pigment excretion*

The essential feature of haemolytic anaemia, however caused, is a shortening of the life of the red blood cell, now known with certainty to be normally about 120 days. In health, therefore, about 0.85 per cent. of the circulating red cells are eliminated from the circulation daily; in haemolytic anaemia, however, the rate of destruction may be increased tenfold or more.

The result of this unusually rapid haemolysis is a greatly increased excretion of bile pigment, almost invariably accompanied by jaundice. The excess bilirubin in the plasma gives a Van den Bergh reaction of the indirect type. In the faeces, the content of bile derivatives, usually measured as 'urobilinogen,' is above the normal daily figure of 80 to 250 mgm. The urine generally contains no bilirubin—the jaundice is 'acholuric,' and only traces of urobilinogen.

In some less common types of haemolytic anaemia blood destruction takes place mainly in the circulating blood stream, and blood pigment may appear in the urine (haemoglobinuria). In the more common types in which haemolysis seems to take place chiefly in backwaters of the main blood stream, such as within the splenic pulp, haemoglobinuria is not seen. In the former instance the patient's plasma may contain considerable amounts of oxyhaemoglobin and methaemalbumin, the haemoglobin in the urine being derived from the plasma oxyhaemoglobin.

(b) *Compensatory red cell regeneration; the bone marrow and the peripheral blood picture in haemolytic anaemia*

Increased haemolysis leads invariably to increased red cell formation within the bone marrow, at least after the first few days of a haemolytic attack, and equilibrium between destruction and formation may be eventually attained. Usually, however, the red cell count is well below normal. Many patients stabilize with haemoglobin levels between 50 and 80 per cent.

This increased marrow activity is accompanied by a centrifugal spread of red marrow into the long bones and a partial or complete disappearance of fat spaces from large areas of marrow, which becomes increasingly hyperplastic and erythrocytogenic. The presence in the peripheral blood of an increased proportion of *reticulocytes* is evidence of this. The reticulocyte count may indeed reach very high levels; sometimes as many as 50 per cent. of the red cells, or even more, are in this form. Macrocytosis is commonly

TABLE 1

THE DUAL PATHWAY OF INCREASED BLOOD PIGMENT EXCRETION IN HAEMOLYTIC ANAEMIA (A SIMPLIFIED SCHEME)

encountered. The cause of this change is uncertain: it may depend in part, at least, upon the increased percentage of reticulocytes present. It is not modified by liver therapy. There may be considerable anisocytosis but poikilocytes are not usually seen, the even roundness and full haemoglobin content of the red cells in haemolytic anaemia being often a striking feature. Microspherocytes are often, but not invariably, present. Nucleated red cells are sometimes seen in the peripheral circulation and have been thought to indicate extra-medullary erythropoiesis. They are, however, rarely present in large numbers (erythroblastæmia). They occur most commonly when the patient is an infant or child; less frequently in an adult (Fig. 1). Immature leucocytes in considerable numbers may rarely be present in the peripheral blood (leukaemoid reaction).

Red Cell Destruction in Health and Disease

A real understanding of the causes and mechanisms of red cell destruction in health would be a great help in the elucidation of what may happen in disease. Unfortunately, even less is known of the former than of the latter. There are four main hypotheses: (a) that red cells are eliminated from the circulation due to the phagocytic activity of reticulo-endothelial cells, (b) that the mechanical trauma to the cells resulting from continuous rapid circulation eventually ruptures the red cell envelopes, (c) that auto-antibodies or chemical haemolysins are responsible and (d) that destruction is due to the effects of stasis in the spleen and elsewhere. The truth is obscure; perhaps some or all the above mechanisms play an integrated

part. In disease, the mechanism may be more obvious. For instance, erythrophagocytosis may be conspicuous in the spleen and in lymph glands, and even in the peripheral blood stream (Fig. 1). Even here the probability is that it is a secondary phenomenon, the cells phagocytosed having been previously damaged by antibody or haemolytic chemical. Certain types of pathological cells such as microspherocytes, sickle cells and probably all poikilocytes and agglutinated cells have been shown to be more easily ruptured than normal by mechanical means. The importance of auto-antibodies is being increasingly revealed; their development is responsible for haemolytic disease of the newborn and many examples of acquired haemolytic anaemia. Stasis within the spleen is probably an important cause of blood destruction in familial haemolytic anaemia (acholuric jaundice).

The truth is that haemolytic anaemia may be caused by a variety of mechanisms, about which enough is now known to justify a pathogenetic classification. Although incomplete and tentative this is preferable to a clinical grouping or one based purely on morphological haematology.

Classification of Haemolytic Anaemias

In the following classification (Table 2) the primary division is between an intrinsic (congenital or acquired) and an extrinsic origin, the former group being divided into those disorders in which the primary abnormality seems to be inherent in the red cells themselves and into those in which the plasma and/or tissues of the patient contain a haemolytic substance secondarily affecting the red cells.

FIG. 1.—Photomicrograph of a blood film from a woman, aged 30, suffering from acquired haemolytic anaemia. Microspheroerythrocytosis, erythroblastæmia and erythrophagocytosis are well shown. The 'Coombs Test' for 'incomplete' antibody was positive. The patient had relapsed after a temporary remission following splenectomy 15 months previously. Jenner-Giemsa X 500.

FIG. 2.—Photomicrograph of a blood film from a woman aged 24 with acquired haemolytic anaemia. An autohaemolysin was present in her serum and an autohaemagglutinin active at 37° C. The photograph shows intense autohaemagglutination and also erythrophagocytosis. Jenner-Giemsa X 600.

FIG. 3.—Photomicrograph of a blood film from a woman aged 61 suffering from polycythaemia vera. She had received an overdose of acetylphenylhydrazine during the course of treatment. The photograph shows contraction and distortion of the red cells and abundant basophilic stippling. Jenner-Giemsa X 600.

TABLE 2

A PATHOGENETIC GROUPING OF HAEMOLYTIC ANAEMIA

(1) *Intrinsic Origin* (congenital or acquired disorders).

A. Due to increased sensitivity of the patient's corpuscles to *normal* mechanisms. The fault lies in the cells themselves.

B. Due to the development of an *abnormal* haemolytic mechanism. The fault lies in the patient's plasma or tissues; the red cells are primarily normal, but may be secondarily altered.

(2) *Extrinsic Origin*. Due to the effects of drugs, chemicals or toxins.

Important haemolytic anaemias belonging to Group 1A of Table 2 are listed in Table 3. Here also might be classified pernicious anaemia and thalassaemia (Cooley's anaemia). In these latter disorders there is an undoubted haemolytic element, possibly secondary to the production of abnormally shaped cells (poikilocytes).

TABLE 3

IMPORTANT TYPES OF HAEMOLYTIC ANAEMIA DUE TO CORPUSCULAR ABNORMALITIES INCREASING THE CELLS' SENSITIVITY TO NORMAL HAEMOLYTIC MECHANISMS

1. Familial haemolytic anaemia (acholuric jaundice).	Congenital origin. Abnormal corpuscles, evidenced by microspherocytes and increased fragility. No plasma abnormalities. Normal cells survive normally after transfusion into patients. Patient's cells survive badly in normal recipients.
2. Sick cell anaemia.	Constitutional origin. Abnormal corpuscles sickled by anoxia. No plasma abnormalities.
3. Nocturnal haemoglobinuria.	An acquired disorder. Abnormal corpuscles evidenced by in vitro lysis in normal sera. Exact abnormality not determined. No plasma abnormalities. Normal red cells survive well after transfusion into patients.

In Table 4 are listed examples of haemolytic anaemia in which an abnormal haemolytic mechanism is known to be the cause of the red cell destruction (Group 1B of Table 2). Auto-antibodies can be demonstrated adsorbed on to the red cells and sometimes in the plasma.

TABLE 4

TYPES OF HAEMOLYTIC ANAEMIA DUE TO AN ABNORMAL HAEMOLYTIC MECHANISM, I.E., DUE TO THE PRESENCE OF ANTI-CORPUSCULAR ANTIBODIES.

1. Acquired haemolytic anaemia.	Not congenital or inherited. Corpuscular abnormalities instant, probably not primary. Auto-antibodies may be present in plasma;

probably always demonstrable on cells. Antibodies usually of the 'incomplete' type. Auto-agglutinins sometimes present; autohaemolysin rarely demonstrable. Normal cells survive badly in patients after transfusion, i.e., they are affected by same haemolytic mechanism as are the patient's own red cells.

2. Haemolytic disease of the Newborn (erythroblastosis foetalis).

Corpuscular abnormalities (spherocytosis and increased fragility) may be present, but not probably primary. Rh auto-antibodies (derived from mother) rarely demonstrable in plasma, but 'incomplete' Rh antibody probably always demonstrable adsorbed on to the affected cells. Normal cells (Rh+) often rapidly eliminated after transfusion.

3. 'Cold' haemoglobinuria.

Corpuscles normal. Auto-haemolysin and haemagglutinin adsorbed from the plasma on to red cells when blood is chilled.

Representative haemolytic disorders due to the action of extrinsic agents (Group 2 of Table 2) are given in Table 5.

TABLE 5

EXAMPLES OF HAEMOLYTIC ANAEMIAS DUE TO EXTRINSIC CAUSES

1. Due to Drugs and Chemicals.	E.g., Sulphanilamide, phenylhydrazine, arsine.
2. Due to Bacterial Toxins.	E.g., <i>Cl. welchii</i> haemolysin (as in puerperal 'gas gangrene').

Mechanism of Haemolysis in Haemolytic Anaemias

In this section will be considered the evidence which has been held to justify the grouping together of the anaemias listed in Table 3.

(A) *Importance of red cell abnormalities*

In *familial haemolytic anaemia* several manifestations of abnormality of the red cells may be demonstrated. Most well known is the increased osmotic fragility, which has been repeatedly demonstrated since first observed by Chauffard 40 years ago; this increase in fragility is held to be associated with the abnormally spheroidal shape of the cells (microspherocytosis). The red cells may also be observed to undergo unusually rapid spontaneous haemolysis when incubated in vitro under sterile conditions (Dacie, 1941), and to be abnormally sensitive to the haemolytic action of lysolecithin (Singer, 1941) and to the effect of

mechanical trauma (Shen, Castle and Fleming, 1944). No abnormalities or antibodies are present in the patient's plasma. The above types of corpuscular abnormality which may be demonstrated in vitro seem to be associated with unusual sensitivity to the action of the spleen—the actual stagnation of blood within the organ may well contribute to this in vivo haemolysis. After splenectomy the cellular abnormalities may be less marked, but rarely disappear. In the absence of the spleen, however, they seem to be relatively unimportant, for the rate of corpuscular breakdown becomes normal or, if not entirely normal, is easily compensated for. The red cell count and haemoglobin content soon rise to the normal levels. The results of transfusion experiments closely parallel in vitro findings. It has been shown that normal red cells survive well in these patients, but the patients' corpuscles both before and after splenectomy are rapidly destroyed in normal recipients (Dacie and Mollison, 1943).

Many similarities exist between *sickle cell anaemia* and familial haemolytic anaemia. In both disorders the fundamental abnormality resides in the red cells themselves. There is an unexplained alteration in the shape of the corpuscles towards sickled forms whenever the level of reduced haemoglobin within the cells increases above a certain critical, but variable, level. The increased rate of haemolysis in vivo is probably due to two factors. The mechanical fragility of sickled cells is considerably increased and actual vascular obstruction may result from the clumping of sickled cells. The patients' plasma is normal. *Nocturnal haemoglobinuria* is a rare but most interesting form of haemolytic anaemia. Once more the corpuscles themselves are at fault. The exact abnormality is, however, obscure; perhaps the cell membranes are defective. The corpuscles behave as if sensitized with haemolytic antibody, for they are readily haemolyzed in vitro by thermolabile components of normal serum (complement), and in vivo by the patient's own plasma. In vitro tests demonstrate that no abnormal antibody exists in the patient's plasma. This has been confirmed by the good survival of transfused normal cells (Mollison, 1947).

(B) *Importance of plasma abnormalities (auto-antibodies)*

In Table 2, Group 1B, are listed three important types of haemolytic anaemia. That termed '*acquired haemolytic anaemia*' has recently received a good deal of attention and ways of distinguishing cases from familial haemolytic anaemia, which it may closely simulate clinically, have been discovered (Loutit and Mollison, 1946). Acquired haemolytic anaemia results from the development of auto-antibodies capable of damaging the

patient's own red cells and accelerating the rate at which they are eliminated from the circulation. The ultimate cause of this auto-antibody formation is quite unknown at the present time. Several types of antibody may be present. The most frequent and important kind seems to be the so-called 'incomplete' antibody, best detected by agglutination of corpuscles on to which this antibody, a globulin, has been absorbed by an anti-human-globulin serum prepared in a rabbit (Coombs, Mourant and Race, 1945). The result of this 'Coombs test' is of great importance in diagnosis. The positive results in acquired haemolytic anaemia contrast with the negative results obtained in the familial disease. Incomplete antibody 'free' in the plasma is seldom detected; presumably it is usually continuously adsorbed on to corpuscles as fast as it is formed. Autohaemagglutinins of the more usual type are sometimes, but inconstantly, present. They are mostly 'cold agglutinins' and seldom active at 37° C. Autohaemolysins are rarely demonstrable. More than one type of antibody effect may be observed in the same patient, incomplete antibody and a high titre cold auto-agglutinin for instance. Clinically the severity and course of the disorder are most variable. Those cases in which haemolysins are demonstrable are particularly severe, and the rapid intravascular haemolysis may be associated with haemoglobinuria. Transfusions with normal blood are of transient benefit; the transfused cells are destroyed rapidly in much the same way as are the patient's own cells (Mollison, 1947). This poor survival is of diagnostic importance and is in striking contrast with the good survival of transfused blood in familial haemolytic anaemia and in nocturnal haemoglobinuria where the fault lies entirely in the patient's corpuscles.

Alterations in corpuscular morphology are often encountered in acquired haemolytic anaemia; macrocytosis is frequent and there is often, but not invariably, spherocytosis and increased fragility of varying grades (Fig. 1). These phenomena are probably secondary events. They sometimes lead to errors in diagnosis. The cause of the increased fragility is obscure; in vitro exposure of cells to the action of agglutinin and haemolysin does not seem to affect fragility. The role of the spleen is likewise uncertain; it is enlarged and palpable, but the enlargement is not on the whole as great as in familial cases. Splenectomy is the only known line of treatment and is often performed. It is usually followed by improvement, and sometimes complete remission. The outlook is, however, uncertain, and the progress of the disease may be hardly influenced. This is not to be wondered at, for the cause of the red cell destruction does not reside primarily within the spleen.

The organ may, however, contribute to haemolysis, by being a source of antibody and by removing damaged cells from the circulation. The ending of activities of this nature may explain the variable benefits which may follow splenectomy.

The exact manner in which 'incomplete' antibody causes haemolysis in vivo is not yet clear. It has been suggested that auto-agglutinated cells are filtered off from the circulation in the spleen and elsewhere, or that the increased mechanical fragility of agglutinated cells may determine their destruction. Further evidence on these points is required. The 'cold' auto-agglutinins active only at temperatures below body temperature are probably of no importance; they may perhaps be looked upon as additional manifestations of the general tendency to auto-antibody development. If active at body temperature they may well contribute to haemolysis, but this is rare (Fig. 2). Autohaemolysins act by damaging the corpuscular surfaces and allowing them to be destroyed by enzyme systems in the plasma (complement).

Haemolytic disease of the newborn. Many of the features of acquired haemolytic anaemia are reproduced in this disorder. Haemolysis is due to the action of antibodies, which may be agglutinins or incomplete antibodies. In haemolytic disease of the newborn, however, the development of antibodies is not auto-genous in the infant; they are of maternal origin, being developed prior to the infant's birth as a result of differences in corpuscular Rh antigens between the unborn infant and the mother. Foetal corpuscular antigens enter the maternal circulation and cause the mother to develop antibodies. These antibodies re-crossing the placental barrier damage the foetal red cells. This sequence of events is so well known that a further discussion would be out of place here. It may be added, however, that as in acquired haemolytic anaemia the exact way in which the antibodies cause destruction of the infant's cells in vivo is far from clear.

Cold haemoglobinuria is a rare but characteristic disorder, usually associated with syphilis, often congenital in type. Intravascular haemolysis and haemoglobinuria occur in episodes, and are brought on by the patient becoming chilled. In the patient's plasma are found 'cold' antibodies (auto-agglutinins and autohaemolysins) which are absorbed on to corpuscles at relatively low temperature, as might be found within the cutaneous vessels in the limbs on a really cold day. The autohaemolysins damage the corpuscular membranes so that the cells become lysed by plasma

enzymes (complement), when they circulate once more within areas of the circulation where the temperature is at or near 37° C.

(C) *Effects of drugs and chemicals*

In Table 5 are listed representative drugs, chemicals and bacterial toxins, all capable of causing haemolysis. The exact way in which some of these drugs and chemicals work is again obscure. Sulphanilamide for instance is inert in vitro and usually in vivo; its occasional haemolytic action in vivo has been thought to be due to the development of unusual derivatives, some of which have been shown to cause increased fragility and ultimately haemolysis in vitro (Emerson, Ham and Castle, 1941).

Phenyhydrazine and acetylphenylhydrazine regularly cause haemolysis in vivo. Morphological evidence of their damaging actions on the red cells can be seen in blood films. Contracted and distorted cells and considerable basophilic punctation may be observed when large doses are given (Fig. 3).

In Cl. welchii septicaemia intense haemolysis may develop, this appears to be due to the action of the α toxin, a lecithinase, on the red cell envelopes.

Summary

Haemolytic anaemia in man is a syndrome of varying causation. A brief description of the main effects of increased haemolysis has been given and this is followed by a tentative grouping of well-known types of haemolytic anaemia into three classes. The primary division is into those of intrinsic and into those of extrinsic origin. The former is subdivided in those disorders in which increased haemolysis seems to be due to corpuscular abnormalities, and into those in which an abnormal haemolytic mechanism is primarily responsible.

This pathogenetic classification is followed by a consideration of the mechanism of haemolysis in certain well-known types of haemolytic anaemia.

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