HAEMOLYTIC ANAEMIA

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In this short review of haemolytic anaemias, general principles of diagnosis and a classification of the various types will be considered first. The well-established advances made during recent years in the understanding of the cause and mechanism of certain haemolytic anaemias will then be surveyed.

The Normal Life Span and Destruction of Red Cells

It is now known with certainty that normal red cells in healthy persons survive about 100 to 120 days. Studies of the rates of disappearance of transfused normal cells (Mollison and Young, 1942), of cells containing sulphamoglobin (Jope, 1946), and of cells containing the nitrogen isotope N15 (Shemin and Rittenburg, 1946) have all given such a value for the life span of a red cell. Little is known of the physiological destruction of red cells at the end of their life, but it is possible that the cells undergo fragmentation and that the fragments are engulfed by the phagocytic cells of the reticulo-endothelial system. The haemoglobin liberated by red-cell destruction is broken down into iron, which is re-utilized, and bilirubin. Most of the bilirubin (but not all of it) is eventually excreted in the faeces as urobilinogen, at least 11 per cent. of the total faecal urobilinogen is derived from sources other than the breakdown of haemoglobin (London et al., 1950). Nevertheless, the amount of urobilinogen in the faeces is a rough guide to the rate of red cell destruction, if considered in relation to the total haemoglobin of the body. Normally, about 11 to 21 mg. of urobilinogen are excreted per day per 100 gm. of haemoglobin (Miller et al., 1942).

The Diagnosis of Haemolytic Anaemia

The haemolytic anaemias are characterized by an increased rate of red cell destruction, the life of the cells being reduced, even to a very few days. Hence large amounts of bilirubin are formed, the serum bilirubin is raised and jaundice is apparent, and the faecal urobilinogen excretion is increased. The urine does not contain bile pigments but larger amounts than the normal traces of urobilinogen are usually present. Occasionally a normal serum bilirubin level is found when a patient's liver can excrete the excess bilirubin without any accumulating in the blood stream.

In response to the increased haemolysis, red cell production is accelerated. The amount of active bone marrow in the body increases together with hyperplasia of the erythropoietic tissue. The proportion of reticulocytes in the blood increases, sometimes up to 50 per cent. of the red cells, and often the large size of these reticulocytes causes a macrocytic blood picture. The normoblasts in the marrow may also be larger than normal—the 'macronormoblasts.' Normoblasts may be found in the peripheral blood, especially in severe examples of haemolytic anaemia and in children, and almost invariably in infants with haemolytic disease of the newborn. Reticulocytes may be almost absent from the blood in 'aplastic' crises (see later). Spherocytes with their characteristic small diameter, increased thickness, and increased osmotic fragility, are commonly seen in haemolytic anaemias, but they are not diagnostic of any one type of anaemia. Marked anisocytosis is often apparent in the blood picture if both spherocytes and reticulocytes are present.

A Classification of Haemolytic Anaemias According to Pathogenesis

(1) Anaemias of Intrinsic Origin
   (a) Due to defects in the red cells. Hereditary, congenital and acquired disorders:
       Hereditary spherocytosis.
       Atypical congenital haemolytic anaemia.
       Sickle cell anaemia.
       Thalassaemia.
       Paroxysmal nocturnal haemoglobinuria.
   (b) Due to the development of abnormal haemolytic mechanisms:
       (1) Caused by auto- or iso-immunization. Acquired disorders:
          Acquired haemolytic anaemia.
Paroxysmal cold haemoglobinuria.
Haemolytic anaemia following virus pneumonia.
Haemolytic disease of the newborn.
(2) Anaemias of uncertain pathogenesis.

(II) Anaemias of Extrinsic Origin
Due to drugs, chemicals, bacterial toxins, etc.: Sulphanilamide, phenylhydrazine, arsine, Cl. Welchii haemolysin, etc.

Anaemias Due to Red Cell Defects
In all these diseases, the plasma is free of abnormal lytic agents and transfused normal red cells survive normally in the patients' circulations. The patients' red cells show no evidence of adsorbed antibodies (i.e. they give negative direct Coombs reactions), but if transfused to a normal recipient, they are rapidly destroyed by the normal haemolytic mechanisms.

Hereditary Spherocytosis
Hereditary spherocytosis (previously called congenital haemolytic anaemia or acholuric jaundice) is characterized by the presence of spherocytes. The normoblasts and reticulocytes are of normal shape, but as the red cells mature, they become thicker and smaller in diameter than normal. This faulty maturation expresses the inborn defect of the cells, the causal gene being inherited as a Mendelian dominant. This disease is inherited and congenital, and is manifest in all grades of severity. The mildest cases have little or no anaemia; hence the introduction of the name Hereditary Spherocytosis. Rarely the spherocytosis is so mild that the osmotic fragility is almost or actually within the normal range. Incubation of the patient's blood will distinguish these cases from normal (see below).

The abnormal shape of the red cells in some way causes them to be trapped and retained in the spleen for varying periods of time (Young et al., 1951b), giving rise to the characteristic large and congested spleen. If blood from a patient is incubated in vitro under sterile conditions at 37° C., the cells increase in osmotic fragility (Young et al., 1951a) and undergo spontaneous lysis or 'auto-haemolysis' (Dacie, 1941) more rapidly than normal. These rapid changes, which may be due to degeneration of the cell membranes, probably occur while blood is stagnating in vivo in the spleen. The spleen is certainly the major site of haemolysis, as its removal invariably results in a complete or almost complete cure of the anaemia. The red cell defect, of course, is unaltered and the spherocytosis persists, although usually to a lesser degree than before splenectomy (Dacie, 1943) as the harmful effects of stagnation in the spleen no longer exist.

A feature of hereditary spherocytosis is the occurrence of sudden relapses, often following infections. The sudden increase in anaemia is, at least in many instances, due to decreased red cell production and not to increased haemolysis (Owen, 1948). Leucocyte and platelet production are also diminished; it is an 'aplastic' rather than a haemolytic crisis.

Patients with hereditary spherocytosis should be advised to undergo splenectomy unless the disease is very mild. The dangers of sudden crises, pigment stores in the gall-bladder, and chronic anaemia are easily outweighed by the prospect of certain relief (if diagnosis is correct), and the present-day risks of splenectomy are small.

Atypical Congenital Haemolytic Anaemia
Occasionally patients are seen with a congenital type of haemolytic anaemia that cannot be classified either as hereditary spherocytosis, sickle cell anaemia, or thalassaemia. These disorders are classified as atypical congenital haemolytic anaemias (Dacie et al., 1953), and they are often familial. The red cell morphology is varied. In many patients the red cells are normally shaped macrocytes (some, but not all, of these large cells are reticulocytes) with occasional oval cells; in others the cells are normal in appearance. Osmotic fragility is not increased and splenectomy has no beneficial effect in the majority of cases. Reports published in the past of patients with congenital haemolytic anaemia who did not benefit from splenectomy were probably of examples of this group or of acquired haemolytic anaemia. Patients with hereditary elliptocytosis occasionally suffer from a haemolytic anaemia, and rarely, patients are seen with small, irregularly shaped red cells that have an increased fragility.

Sickle Cell Anaemia
Sickle cell disease, which is inherited and congenital, exists more commonly as a trait, when no haemolytic anaemia is present and the person's red cells undergo sickling only under artificial conditions. Probably persons with the trait possess the sickle gene in the heterozygous state, and persons with sickle cell anaemia possess the gene in the homozygous state (Neel, 1951). If a child has sickle cell anaemia, then both parents should exhibit the trait. From 20 to 45 per cent. of the haemoglobin of persons with the trait, and 80 to 100 per cent. of the haemoglobin of persons with the anaemia is an abnormal 'sickle haemoglobin' (Pauling et al., 1949, Wells et al., 1950). The fully oxygenated red cells of sickle cell anaemia are normally shaped; but when de-oxygenated, the reduced sickle haemoglobin has such a low
solubility that it undergoes crystallization within the cells and so distorts the cells into the peculiar sickle shape (Perutz and Mitchison, 1950). On re-oxygenation, many cells resume their normal shape, but others remain irreversibly sickled. It is thought that sufficient intermittent or continuous stagnation of the blood in various organs of the body with consequent sickling of the cells may result in the production of irreversibly sickled cells. Sickled cells have a greatly increased mechanical fragility and a shortened life span (Singer et al., 1948). Cells from persons with the trait have a normal life span.

The occasional finding of a child with a sickle cell anaemia but only one parent with the trait, has probably been explained by the recent discoveries that the non-sickling parent may have: (1) only small amounts of sickle haemoglobin in the cells, insufficient to cause sickling even under artificial conditions (Singer and Fisher, 1953); (2) another abnormal haemoglobin, such as 'haemoglobin c', in the cells—a disease resembling sickle cell anaemia arises in the children who inherit the haemoglobin c trait and the sickle trait (Kaplan et al., 1951); (3) the thalassaemia trait, which also causes an anaemia due to sickling when inherited with the sickle trait (Powell et al., 1950).

**Thalassaemia**

Thalassaemia is again an inherited and congenital disease, the thalassaemia gene in the homozygous state causing thalassaemia major or Cooley's anaemia, and in the heterozygous state causing thalassaemia minor. This gene apparently inhibits the synthesis of normal adult haemoglobin, the red cells being hypochromic and microcytic, and target cells are common. The osmotic fragility is reduced. The minor disease varies in severity from a condition with moderate anaemia to one with no anaemia in which the life span of the cells is normal (Kaplan and Zuelzer, 1950). Cases of the major disease have a severe anaemia and the red cells show a marked degree the abnormalities mentioned above. These cells have an increased mechanical fragility and readily undergo fragmentation with a resultant decrease in life span. The results of splenectomy, as in sickle cell anaemia, are usually poor.

Small amounts of the haemoglobin in the minor disease and moderate amounts of the haemoglobin in the major disease are foetal haemoglobin (Singer et al., 1951). The persistence of this haemoglobin after the first year of life may reflect the failure to synthesize adult haemoglobin in normal amounts.

**Paroxysmal Nocturnal Haemoglobinuria**

Manifestations of paroxysmal nocturnal haemoglobinuria usually appear in adult life. The red cells apparently acquire a defect of unknown nature; their osmotic and mechanical fragilities are normal. The cells become sensitive to and are haemolyzed by a component of normal serum (Dacie, 1949), similar to but not identical with complement (Crosby, 1953). This component, which is inactive against normal red cells, acts on the patients' cells in vitro with an optimum pH of about 7.0 (i.e. slightly to the acid side of the physiological pH). It is usually inactive at pH 8.0, which is about the pH of serum samples collected in the usual way with loss of carbon dioxide into the air. For some reason, which is not clear, the red cells undergo more haemolysis in vivo when the patients are asleep than when awake. The haemolysis is intravascular, haemoglobin being released into the plasma and partly excreted into the urine (haemoglobinuria).

**Anaemias Due to Abnormal Haemolytic Mechanisms**

**Acquired Haemolytic Anaemia Due to Auto-immunization**

Probably the majority of patients with an acquired type of haemolytic anaemia belong to this group. The characteristic feature is the development of abnormal auto-antibodies active at body temperature. In most patients the cause of this is unknown. The most common type of auto-antibody is a warm incomplete or 'sensitizing' antibody, optimally active at 37°C. The patients' red cells have no inborn defect, but they adsorb large amounts of the antibody that is released into the blood stream, thereby becoming 'sensitized' and giving positive direct Coombs' reactions. The serum itself usually contains small amounts of free antibody, detectable in several ways, e.g. by the indirect Coombs' test or the use of trypsinized red cells (Dacie and de Gruchy, 1951). This sensitization of the patients' cells, if sufficient in degree, leads to rapid destruction of the cells in vivo. The importance of the degree of sensitization can be demonstrated if sensitized cells from patients with acquired haemolytic anaemia are transfused to normal recipients; some of the cells are rapidly destroyed, but most of them lose some but not all of their adsorbed antibodies whilst circulating in the normal environment and survive normally (Selwyn and Hackett, 1949). Hence, it is thought that the cells in a patient's blood stream adsorb increasing amounts of antibody until a certain critical degree of sensitization is reached and then they are destroyed. Normal cells transfused to patients with acquired haemolytic anaemia adsorb the sensitizing antibodies in the same way and are therefore also
destroyed more rapidly than normal. The mechanism of destruction is uncertain; one probable mechanism is the phagocytosis of the sensitized cells in the spleen and other organs. The cells of about 75 per cent. of the patients show spherocytosis, a secondary change due to the action of antibodies; this change also appears to lead to haemolysis in the spleen and elsewhere.

Splenectomy produces a remission of the haemolytic anaemia in only about 50 per cent. of patients (Dameshek, 1950). For this and the following three reasons, it should be considered only as a last resort in the treatment of a patient. Firstly, spontaneous remissions occasionally occur and can be apparently permanent. Secondly, certain neoplastic conditions (e.g. chronic lymphatic leukaemia and reticulo-sarcoma) are occasionally associated with a secondary haemolytic anaemia due to auto-antibodies. The neoplasm may be obscure and may not become apparent until after the haemolytic anaemia has been present for some while. Thirdly, and most important, the administration of ACTH or cortisone in sufficient dosage results in a moderate or complete relief of anaemia in the majority of patients, together with a decrease in the degree of sensitization of the red cells (Dameshek, 1952). These remissions are probably due to inhibition of the production of antibodies and last for varying periods of time. Hence treatment with ACTH or cortisone should have a thorough trial before splenectomy is considered.

The sera of patients with acquired haemolytic anaemia may contain moderately strong cold auto-antibodies which are inactive at body temperatures. Occasionally, however, patients are seen with no warm auto-antibodies in the blood; instead, their sera contain potent cold antibodies optimally active in the cold but with a high thermal range. The cold incomplete antibodies are active even up to 37°C, thereby sensitizing the patients' red cells in vivo and causing a chronic haemolytic anaemia. The cold agglutinins have a smaller thermal range, but in rare cases they are active up to temperatures just below 37°C and they may agglutinate the red cells in vivo with resultantRaynaud’s phenomena if the body extremities are severely chilled (Ferrimen et al., 1951). Severe chilling may also be followed by an episode of intravascular haemolysis and haemoglobinuria. This haemolysis is probably due to the increased mechanical fragility of agglutinated cells and to the direct lysis of these cells by complement. The lysis by complement can be demonstrated in vitro, but in most cases only if the sera are acidified to about pH 7.0 (Dacie, 1950). This type of haemoglobinuria is not associated with syphilis.

**Paroxysmal Cold Haemoglobinuria**

Paroxysmal cold haemoglobinuria is a rare disorder, characterized by episodes of intravascular haemolysis which take place when the patient has become chilled and by the consequent haemoglobinuria. A chronic haemolytic anaemia is usually not present, and in most, but not all, cases the patients have a syphilitic infection. The sera of all patients contain the Donath-Landsteiner lymph. This lysin (demonstrable in vitro with unacidified sera) is adsorbed with complement on to the patients' red cells in the cold; the cells are lysed by further amounts of complement when they circulate again in warm parts of the body.

**Haemolytic Anaemia Following Virus Pneumonia**

The hightitre auto-antibodies commonly found in the sera of patients with virus pneumonia may occasionally cause an acute haemolytic episode in the later stages of the illness if they have a sufficiently high thermal range (Dacie and de Gruchy, 1951).

**Haemolytic Disease of the Newborn**

The causal antibodies of haemolytic disease of the newborn are formed in the mother and are iso-antibodies, active against particular blood group factors. Further consideration of this disease will have to be omitted from this review.

**Anaemias of Uncertain Pathogenesis**

Haemolytic anaemias secondary to neoplastic disease, or more rarely, with no apparent cause, can occur with no evidence of auto-antibody formation. Patients in the terminal stages of uremia sometimes show signs of increased haemolysis. The mechanisms of haemolysis in these cases are quite unknown.

**Anaemias Due to Drugs and Chemicals**

The exact way in which certain drugs and chemicals can cause haemolysis in vivo is again obscure. Probably both hypersensitivity and direct toxic action can play a part. Spherocytic and distorted red cells are often found. Drugs of the sulphonamide group, especially sulphanilamide, are important causes of such haemolytic anaemias. Phenylhydrazine and many other benzoic acid compounds cause the formation of Heinz inclusion bodies in the red cells (Webster, 1949; Wells and Etano, 1950). These bodies are particles of denatured haemoglobin and apparently the affected cells are destroyed in the spleen.

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cases of chronic myeloid leukaemia seem to be more satisfactory and longer lasting than those usually obtained after treatment with other drugs. In a few cases remissions can be obtained after the disease has ceased to respond satisfactorily to irradiation and reduction of troublesome and radio-resistant splenic enlargement will follow Myleran treatment in most instances. Myleran is useless in acute leukaemia and in the acute myeloid crisis of chronic leukaemia.

The dose of Myleran should not exceed 4 mg daily. During the second or third week the leucocyte count begins to fall, but normal levels may not be reached before three or four months. The treatment is continued with frequent blood-count control, provided that the improvement is maintained and that there is no reduction of platelets to less than 100,000 per cu. mm. Higher doses of Myleran are likely to cause thrombocytopenia or general marrow aplasia.

As in TEM, experience is as yet too restricted to be certain that the prolonged administration of Myleran has no deleterious effect on normal marrow function and the use of these drugs might therefore remain confined for the present to cases in which irradiation or nitrogen mustards are contra-indicated or are no longer effective.

Radiotherapy and the present forms of chemotherapy in leukaemia act by a purely repressive or destructive effect on malignant cells. The selectivity of this effect is only one degree of the hope for the future must lie with the development of methods which will either damage malignant cells exclusively, or better still, restore the normal control-mechanism which regulates mitosis and differentiation of cells in accordance with the needs of the body.

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