CLINICAL PATHOLOGY IN GENERAL PRACTICE

INVESTIGATION OF HAEMOLYTIC ANAEMIA

BY

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Red cells are normally removed from the circulation within 120 days, a process which involves the daily destruction of some 2.7×10^{11} erythrocytes in a man with a blood volume of 5 litres. An equivalent number of newly formed cells are provided by the bone marrow, which is able within certain limits to increase its rate of red-cell production as required. Thus, the marrow can cope with sudden extra demands caused by abnormal red-cell destruction or loss, and the presence of a mild haemolysis may be obscured; when red-cell destruction becomes too great for full replacement to be achieved by marrow hyperplasia, then a haemolytic anaemia becomes manifest.

Clinical Types

Haemolytic anaemias form a group of blood diseases, not easy to classify, caused by a variety of intrinsic and extrinsic factors producing excessive red-cell destruction. In general, the acute or subacute haemolytic anaemias are due primarily to extrinsic factors, while most of the chronic types have familial or hereditary features and the red cells themselves may be abnormal; in the latter group we find, among others, acholuric jaundice and familial haemolytic spherocytic anaemia (with spherocytes), sickle-cell anaemia (with sickle cells), thalassaemia or Cooley's anaemia (with leptocytes or target cells).

The acute haemolytic anaemias may be caused by the toxic or haemolytic effects on the normal red cells of severe bacterial or protozoal infections—for example, septicaemia, malaria—many chemical poisons such as compounds of arsenic, lead, bismuth, silver, and phosphorus; chlorates and methyl chloride; derivatives of benzene and toluene (aniline, phenylhydrazine, acetanilide, sulphonamides); haemolytic agents such as saponin, lysolecithin, snake venom, and *Vicia fava*, the broad bean. Severe acute haemolytic anaemias also arise following incompatible blood transfusions (α and β agglutinins), the production of anti-Rh agglutinins causing, for example, erythroblastosis foetalis, and in the presence of cold iso-haemolysins. Acute or subacute haemolytic anaemia may also be a secondary feature to other conditions such as Hodgkin's disease, carcinomatosis, hypersplenism, and leukaemias among others.

While the severity of the haemolytic process may modify the symptoms, in general all these haemolytic anaemias clinically show a varying degree of jaundice and evidence of excessive red-cell destruction; there will be the usual general symptoms associated with, and proportionate to the degree of, anaemia; haemorrhagic or haemolytic manifestations may occur, and pigment gall-stones are common. Pyrexia, malaise, headaches, and haemoglobinuria may be noted; the spleen is often enlarged, the liver less often, and occasionally also the lymph nodes. Glossitis, neurological symptoms and signs, and flatulent dyspepsia are not seen, in contrast to their occurrence in pernicious anaemia, although sometimes there are other gastro-intestinal disturbances. In mild cases, on superficial clinical examination, the patient may appear to be suffering from pernicious anaemia or cholecystitis until blood and other examinations have disclosed the true condition.

The essential laboratory investigations in a case of haemolytic anaemia include a full blood count with estimation of daily reticulocytes, estimation of the osmotic fragility of the red cells, bone-marrow biopsy, examination of the gastric juice, and a search for abnormal agglutinins in the blood. Subsidiary tests may include estimations of faecal and urinary urobilinogen, and special tests for specific agglutinins or other haemolytic factors.

Blood Count and Osmotic Fragility

It is important to make a full blood examination, including reticulocyte and differential white-cell counts and an estimation of the osmotic fragility of the red cells. The anaemia, which is usually macrocytic but may be normocytic or less commonly microcytic, may be severe (R.B.C. 1,000,000 to 2,000,000, and Hb 2.3 to 5.9 g. per 100 ml.). The severity varies with intermittent remissions and frequent crises. One of the most striking and diagnostic features is the notable reticulocytosis (10 to 80%) that may persist with varying severity for many months or years. Reticulocytosis with anaemia, in the absence of haemorrhage or treatment with liver, iron, etc., and persisting for weeks or months despite treatment, is almost pathognomonic of a haemolytic anaemia. It is common to find normoblasts, but rarely megaloblasts, in the peripheral blood. Many of the red cells have a bluish tinge (polychromasia) reflecting their immaturity. Small darkly staining red cells (microspherocytes) are often seen in acholuric jaundice.

The osmotic fragility of the red cells varies in different patients, and the sizes and shapes of the cells depend on the particular type of anaemia. An accurate quantitative fragility test is necessary to detect the mild forms of chronic haemolytic anaemia (acholuric jaundice). The old method of reading the haemolysis visually is inaccurate and has been replaced by the quantitative method of estimating the liberated haemoglobin in the various hypotonic solutions by means of a photoelectric colorimeter. While a significant increase in the red-cell osmotic fragility is pathognomonic of a haemolytic anaemia it does not indicate the particular type other than a spherocytic haemolytic anaemia; a variable increase is found in many but not in all haemolytic anaemias of acquired type, as well as in the classical familial chronic type.

A slight leucocytosis or occasionally a leucopenia with a few immature white cells (myelocytes and myeloblasts) may be seen, perhaps occasioning some difficulty in differentiating the condition from acute leukaemia. The marrow picture in these cases is of great value, for the absence of a significant number of "blast" or "stem" cells excludes an acute leukaemia. The platelets are usually normal in number but may be decreased in patients in whom haemorrhages are occurring.

To demonstrate sickle cells it is necessary to reduce the oxygen tension of the blood by sealing a drop under a cover-slip; sickle-cell haemoglobin becomes crystalline with deoxygenation, loses water during the process of crystallization, and so changes its shape and becomes sickle-shaped. A person in whose blood sickle cells can be demonstrated, but who shows no obvious signs of haemolysis, is said to have the sickle-cell trait. In thalassaemia (Cooley's anaemia) many of the red cells have a "target appearance" (target

cells); adults usually exhibit mild or symptomless forms known as thalassaemia minor; the complete major disease is usually fatal in childhood.

Bone-marrow Biopsy

Examination of the marrow is a necessary step in the diagnosis of many of the haemolytic anaemias, for it helps to exclude leukaemia, pernicious anaemia, and other conditions having similar clinical and blood findings. In haemolytic anaemia there is a marked hyperplastic marrow reaction with large numbers of early basophilic, intermediate, and late normoblasts. Proerythroblasts may also be increased in number. In the long-standing haemolytic anaemias the normoblasts may show changes in nucleus and cytoplasmic details that differ somewhat from those seen in other macrocytic anaemias, for there may be many mitoses present in the prematurely haemoglobinized cells. The myeloid-erythroid ratio is often less than unity, the total nucleated red cells constituting 60 to 80% of the total nucleated count. Megaloblasts are rarely found. Activity in the granulocytic and megakaryocytic series may be observed, although there may be a total reduction in their number.

Blood Pigments

A normal serum does not give a direct van den Bergh reaction and contains not more than 1 mg. of bilirubin per 100 ml. In haemolytic diseases, jaundice is due to the liver cells being unable to excrete fast enough the increased bilirubin formed from the excessive breakdown of haemoglobin. The van den Bergh reaction is based on the hypothesis that bilirubin reacts differently with the diazo-reagent according to whether or not it has been excreted by the liver cells. Bilirubin formed from haemoglobin has been termed *indirect* bilirubin, since it does not give an immediate direct reaction. Bilirubin which has been excreted by the liver cells (as is found in the blood in obstructive jaundice) gives an immediate direct reaction and has been termed *direct* bilirubin. In haemolytic jaundice there is an increase in *indirect* bilirubin so that indirect reactions or direct delayed reactions are obtained. In some forms of haemolytic disease the agent acting on the red cells may also have a toxic action on the liver cells, in which case a biphasic reaction may be reported.

In acholuric jaundice the serum bilirubin may rise as high as 16 mg. per 100 ml., and in some forms of acute haemolytic anaemia similar or higher values may be obtained. The quantitative estimation of serum bilirubin is useful in sub-clinical jaundice, the demonstration of small increases in serum bilirubin to between 1 and 2 mg. per 100 ml. is usually of diagnostic value. When intravascular haemolysis is rapid, haemoglobin and methaemalbumin are found in the peripheral blood. This occurs in some severe haemolytic anaemias (blackwater fever, septicaemia, incompatible transfusion) and in the paroxysmal haemoglobinurias.

Haemoglobin appears in the urine when the plasma level is over about 130 mg. per 100 ml. Haemoglobin liberated in the plasma is partly excreted as haemoglobin in the urine, and some is converted into methaemalbumin. The presence of methaemalbumin in the serum shows that intravascular haemolysis has occurred. Methaemalbumin does not appear to be formed when there is increased breakdown of haemoglobin in the reticulo-endothelial system. It is found in the plasma in malaria, and in many of the acute haemolytic anaemias in which the haemolysis is intravascular, but not in acholuric jaundice and such conditions in which the haemolysis is non-vascular. Methaemalbumin has a large molecule and is excreted by the liver as coproporphyrin III.

Urinary and Faecal Urobilinogen

Urobilinogen is formed in the intestines by the reduction of bilirubin, and thus the amount of faecal urobilinogen depends on the amount of bilirubin entering the intestines.

Faecal urobilinogen (normal 40–280 mg. a day) is increased in haemolytic anaemias in which there is

increased breakdown of haemoglobin to bilirubin. In acholuric jaundice and chronic haemolytic anaemias values of 500 to 1,500 mg. may be obtained. The dark colour of the faeces in these conditions is due to the large amount of pigment present.

Urinary urobilinogen (normal 0.5–2 mg. a day) is derived from the urobilinogen absorbed from the intestines and not excreted by the liver. The amount depends both on the quantity of bilirubin entering the intestines and on the capacity of the liver to excrete the urobilinogen coming to it from the intestines. In haemolytic diseases the urinary urobilinogen tends to be a little raised, since the liver is unable completely to excrete the increased amounts of urobilinogen absorbed from the intestines. Values up to 10 mg. a day are usually found.

Whenever there is active blood regeneration in the haemolytic anaemias coproporphyrin I appears in the faeces. In compensated haemolytic disease in which there is no appreciable anaemia an increased excretion of faecal urobilinogen may be the only confirmatory evidence of a haemolytic process.

The *haemolytic index* (normal 11–20) is sometimes determined in children, in whom the total circulating haemoglobin is less than in adults. The index is found from the following equation:

$$\frac{\text{Average daily output of faecal urobilinogen} \times 100}{\text{Total Hb (g. per 100 ml.)} \times \frac{\text{Total blood volume}}{100}}$$

It is a time-consuming investigation and is seldom used for routine clinical work.

Auto-immunization

The cause of the haemolytic state in a variety of diseases is the production of antibodies against the patient's own red cells (auto-antibodies). In many of these cases no reason for this can be demonstrated, but in others an associated disease is found and in these the condition is symptomatic. Many of the reticuloses, chronic lymphatic leukaemia, Hodgkin's disease, periarteritis nodosa, and disseminated lupus erythematosus are primary causes of auto-immune haemolytic disease.

The way in which antibodies bring about haemolysis is not certain. In some cases haemolysins appear which produce haemolysis in the presence of complement. In others, with a high concentration of cold haemagglutinins, haemolysis occurs after cooling. The abnormal antibody in most cases of acquired haemolytic disease is a haemagglutinin which can be demonstrated by the Coombs test or by suspending the sensitized cells in a protein medium (bovine albumin). The nature of these antibodies is such that agglutination will not take place if saline is used as the medium for suspending the red cells.

The Coombs test is used to detect the presence of incomplete antibodies* in the serum and to help in the diagnosis of haemolytic disease of the newborn by demonstrating that the infant's corpuscles have absorbed the antibody. To identify such antibodies Coombs prepared an anti-human globulin serum by injecting human globulin into rabbits. When red cells sensitized by a non-agglutinating antibody are washed in saline and then suspended in the antiglobulin serum they become agglutinated.

In most cases of idiopathic acquired haemolytic anaemia the Coombs test is positive, indicating the presence of globulin antibodies adsorbed to the surface of the red cells, and in these cases no agglutination occurs in saline-serum suspensions. Agglutination may also be demonstrated by suspending the cells in a colloid such as bovine albumin, but the Coombs test is thought to be more sensitive and is more commonly employed.

Trypsinized red cells were found to be good indicators of incomplete antibodies, and do not require a protein medium

*An antibody that agglutinates red cells only in the presence of albumin or plasma and in the absence of sodium chloride.

for suspending the cells. Many of the abnormal incomplete agglutinins are haemolytic when incubated with complement against trypsinized red cells.

Haemoglobinuria

Patients with haemoglobinuria have a haemolytic disease and present many of the features associated with the haemolytic syndrome. Several varieties of paroxysmal cold haemoglobinuria are recognized.

With a Cold Auto-haemolysin.—This type occurs most frequently as a complication of syphilis, either congenital or acquired. It is characterized by haemoglobinuria following exposure to cold. The Donath–Landsteiner test is diagnostic of cold haemoglobinuria. In this test, red cells suspended in the patient's serum are exposed to a low temperature so that the cold haemolysin may be absorbed, and then to a higher temperature so that haemolysis may be completed by the action of the serum complement. Normal red cells can be used in this test. In life the haemolysin becomes fixed to the red-cell surface during exposure to low temperatures, and when the blood circulates and becomes warmer haemolysis occurs.

With Cold Agglutinins.—Raynaud's syndrome, with acrocyanosis and pain in the extremities, may occur in paroxysmal cold haemoglobinuria associated with cold agglutinins. When titrated, the cold haemagglutinin may exceed 1/1,000 and rarely be demonstrated at up to 1/100,000. Cold haemagglutinins have been found in a number of conditions not necessarily associated with demonstrable haemolytic disease. In atypical pneumonia, for instance, they are often reported to be present.

Paroxysmal Nocturnal Haemoglobinuria

In this chronic haemolytic disease, haemolysis becomes intensified during sleep and nocturnal haemoglobinuria occurs. The patient's corpuscles are sensitive to thermolabile components of normal serum, but acidification is necessary to bring the pH of the cell-serum suspension to about pH 6.8 before the serum factors will act. This is the principle of the Ham test which is employed to diagnose this condition. Acidification is necessary because defibrinated blood becomes slightly alkaline owing to loss of carbon dioxide. Clinically, patients with nocturnal haemoglobinuria show an abnormal sensitivity to minor changes in blood pH. This may also be a factor in other haemolytic mechanisms.

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According to the Eighth Annual Report of the Institute of Child Health, the number of full-time students in 1953 was just under one hundred and there were also 40 part-time students. While most of the students attending were from the Commonwealth, it is interesting to note that 14 full-time students were from countries outside the British Empire. This perhaps signifies the growing importance of London as a postgraduate centre. More emphasis was laid in 1953 on clinical instruction. The number of lectures was reduced and opportunities were provided for increased ward teaching. Arrangements were made for small groups of two or three students to "sit in" with registrars during the out-patient sessions.

BEDSIDE MANNERS

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A dermatologist told the following story. A patient came to him with eczema in one axilla. A previous doctor had told the patient that the eczema was due to sweating. "I sweat here and I sweat there," the patient argued, pointing to his two axillae; "how can the eczema be due to sweating?" "What do you think it is due to?" the dermatologist asked. "I believe," the patient said, "that it is due to sugar diabetes." "You would have sugar diabetes here and there," the doctor said, pointing to the patient's two axillae, hence you can't have sugar diabetes." Subsequently the patient felt greatly relieved, and incidentally the eczema disappeared. The patient was extremely grateful.

This story serves to introduce the subject of this paper—"bedside manners" and psychotherapy. Bedside manners may be defined as an unsystematized understanding of a patient's emotional needs, whereas psychotherapy is their conscious systematized counterpart.

Systematic psychotherapy is predominantly the domain of the psychiatrist; bedside manners is a term applied to the intuitive approach used by general practitioners and specialists not specifically trained in psychiatry. Both bedside manners and psychotherapy are based on interaction between patient and doctor. It is proposed to discuss some of the more common psychological problems of patients and doctors, and some principles governing reciprocal physician-patient relationships.

The Patient

A patient is a person who seeks the help of a physician because he deviates in mental or physical health from the norm. He is not necessarily a sufferer as the word patient connotes. In view of his sickness a patient has to assume a role which imposes on him in many cases the necessity of forgoing his usual activities, of retiring to bed, and of accepting another person's help to restore him to his previous state of health. If he is very sick he may have to abandon his functional status of an adult and perhaps be attended to in a baby-like fashion.

Research in psychosomatic medicine has shown that emotional factors often play an important part in the aetiology of so-called "organic" diseases. Be this as it may, in any given patient illness as such, and the change in mode of living which it comprises, leads to a backward movement towards earlier stages of emotional development and behaviour. This state of regression, as it is called, manifested by changed attitude and feelings, is particularly significant in chronic illness. It may have the following interrelated effects: (1) patients may become childish in their behaviour; (2) they may, and usually do, become selfish; (3) they may invest the interest which they withdraw from the external world on the affected part of the body and consequently develop superadded hysterical or hypochondriacal formations; (4) they may distort reality