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Professor Ronald H. Girdwood
M.D., Ph.D., F.R.C.P., F.R.C.P.Ed., F.C.Path.

Abstract
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For this reason it is necessary to approach the subject in a manner somewhat different to that employed by other writers in the current series of articles, and to stress particularly the importance of both the history and the laboratory investigations.

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THE INVESTIGATION OF A PATIENT BELIEVED TO HAVE A BLOOD DISORDER

by Professor **RONALD H. GIRDWOOD, M.D., Ph.D., F.R.C.P., F.R.C.P.Ed., F.C.Path.**

University Department of Therapeutics, Royal Infirmary of Edinburgh

One of the difficulties of writing an article on this subject is that of finding a suitable title, since one is not dealing with a system of the body in the usual sense of the term, but, instead, with a number of conditions which are related only in that an abnormality exists either in the formed elements or the clotting mechanism of the blood. Accordingly there is a great variation in the spectrum of possible physical abnormalities and, indeed, there may be a serious blood disorder with neither symptoms nor signs.

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THE HISTORY

It may be that there is no history of illness and that a person who feels perfectly fit and who for some reason has had a routine blood examination carried out is found to have even such a serious disease as leukaemia. Fortunately, such an event occurs but rarely. At the other end of the scale is the child who is brought for examination because there is a family history of haemolytic anaemia or of haemophilia, and the parents are anxious to be assured that their offspring has escaped the abnormality.

In most instances the patient goes to a doctor because of dizziness, fatigue, dyspnoea, palpitations or pallor and a diagnosis of anaemia is considered. However, it is the experience of clinicians in charge of blood clinics that quite a large proportion of the patients referred to them have somewhat similar symptoms but are not anaemic. Pallor is not uncommon in hypertension and the patient with a high blood pressure may suffer from dyspnoea and tiredness.

The points of importance in the history are many, a full physical examination is usually necessary, and the possible laboratory investigations are legion. In the first instance, however, it is necessary to narrow the field as far as possible. It may be that the conjunctivae indicate, without doubt, that the patient is anaemic and the reason for this may become obvious from close questioning. It is, however, desirable to have at least a haemoglobin estimation performed before going into details of history or examination. Meantime, if at all possible, a white cell count should be obtained and a blood film prepared.

The Anaemic Patient

Mention has already been made of features that are common to the various forms of anaemia. It is sometimes possible to deduce from the history and a superficial examination the type of anaemia that is present, but it is easy to make mistakes and always necessary to carry out further investigations to confirm or disprove clinical impressions.

If the patient is anaemic, the most likely causes are:—

(a) Iron deficiency.

(b) Deficiency of vitamin B_{12} or folic acid.

Also possible, but less common, are:

(c) Excessive haemolysis.

(d) Marrow failure or replacement.

Other conditions that must be considered include myxoedema, uraemia, hepatic cirrhosis, chronic infection, and malignancy.

Pointers of importance in the history are:

Iron deficiency. There may be a history of chronic blood loss, most commonly from heavy periods. Other possibilities include bleeding haemorrhoids, a diaphragmatic hernia and the repeated taking of aspirins either as such or in some proprietary preparation by a patient who is sensitive to the drug. Chronic bleeding from a peptic ulcer is less common than is sometimes believed, but a carcinoma of the stomach or large intestine must always be borne in mind. Almost half the patients who undergo partial gastrectomy develop iron deficiency anaemia, and details of operations must be included in questions about the history. In this country primary malnutrition is uncommon, but once it is established that iron deficiency exists, a brief dietetic history and perhaps thereafter a detailed one may be necessary. Portal hypertension is commonly associated with iron deficiency anaemia and the history is frequently unhelpful. Difficulty in swallowing is uncommonly a feature of iron deficiency anaemia and when it occurs in association with anaemia or glossitis the term Kelly-Paterson or Plummer-Vinson syndrome is frequently used. It should be remembered, however, that difficulty in swallowing may be due to a carcinoma of the oesophagus or to one of a variety of other causes. With the increase in immigrant population the possibility of a haemoglobinopathy or thalassaemia, which is not a true haemoglobinopathy, must be remembered as a reason for hypochromic anaemia that does not respond to treatment. It is rarely that a family history of such conditions is known by the patient.

Deficiency of vitamin B_{12} or folic acid

Vitamin B_{12} deficiency may occur because of primary malnutrition (seen in this country only in the extreme vegetarian group known as Vegans), lack of intrinsic factor (pernicious anaemia, partial gastrectomy and, very rarely, other operations on the stomach), malabsorptive states (including gluten enteropathy, tropical sprue, organic disease of the small intestine and resection of the lower ileum — this is the area in which absorption of vitamin B_{12} occurs) and, finally, so far as Great Britain is concerned, blind or stagnant loops of small intestine which become colonised by bacteria.

Accordingly the points in the history that are of importance are:

Whether the patient is a Vegan — an unlikely possibility.

Whether there has been a gastric operation or, less likely, small intestinal resection.

A family history of pernicious anaemia.

A history of diarrhoea or other evidence of a disorder of the small intestine.

Complaint of a sore tongue. This also occurs in iron deficiency, but such symptoms are then usually less severe. It can also be a symptom of deficiency of riboflavin, nicotinic acid or folic acid. It is very rare in this last, and the other two deficiences are seldom encountered in the United Kingdom.

A history of paraesthesiae or of difficulty in walking (possible subacute combined degeneration of the cord).

Folic acid deficiency

Folic acid deficiency is caused by primary malnutrition, pregnancy, malabsorption or, sometimes, the giving of anticonvulsant drugs. Other causes are rare.

It is therefore necessary to question the patient about:

Diet — folic acid deficiency is being reported increasingly amongst old people in the United Kingdom.

Pregnancy.

The taking of anticonvulsant drugs.

Symptoms of small intestinal disease, particularly diarrhoea or steatorrhoea.

Excessive haemolysis

There are, of course, various extremely rare forms of haemolytic anaemia, and, in fact, all varieties are seen here but seldom. The most likely possibilities are congenital spherocytosis, idiopathic acquired haemolytic anaemia, or drug induced haemolysis. In haemolytic anaemia (which is also known as acholuric jaundice), the yellow colour of the sclerae or skin may be obvious, and the first diagnostic problem may be not so much to find the cause of obvious anaemia as to ascertain the reason for obvious jaundice. Indeed, there may be no anaemia at all.

The questions to be asked in the history in relation to haemolytic anaemia are:

The family history of the condition: however this may not be present.

Whether or not the faeces are normal in colour.

Whether the patient has been taking drugs, particularly sulphonamides, nitrofurantoin or methyldopa.

It should be remembered that acute crises may occur in patients with spherocytosis, sometimes in more than one member of an affected family at the same time. This may indicate that the crises are induced by an infection, but, in any event, a history of sudden weakness, breathlessness, rigors, increased pallor and jaundice is likely to indicate that a crisis has occurred. This, fortunately, is rare.

Marrow failure or replacement

Anaemia may occur because the bone marrow is infiltrated with malignant cells, including those of leukaemia, or with fibrous tissue in the rare condition of myelofibrosis. It may be, however, that the patient has true aplastic anaemia which may be idiopathic but is more commonly due to an idiosyncrasy to a drug or chemical, and similar causes must be sought in thrombocytopenia and agranulocytosis. In taking the history, therefore, it is important to ask about the taking of drugs or exposure to chemicals . In particular, very close questioning should be carried out about the possible taking of chloramphenicol in the preceding nine months. Great care must be taken in this part of the history taking and repeated leading questions may be required before the patient remembers what has been taken. It will possibly be necessary to consult the patient's general practitioner if a patient is being investigated in hospital, and the employers may have to be approached to give information about chemicals. As an example of the difficulties, a patient seriously ill with aplastic anaemia and who could not remember having received any drugs eventually remembered that she had gone into a chemist's shop while on a bus tour of Switzerland and there had purchased some tablets for a headache. The container was recovered, and the tablets found to contain amidopyrine, a notorious cause of blood dyscrasias.

Other Causes of Anaemia

It is important to remember the possibility of myxoedema and uraemia, two conditions which may easily be overlooked. The incidence of myxoedema (and also of thyroiditis and hyperthyroidism) is increased in pernicious anaemia, and it is important to ask whether the patient prefers cold or heat, is gaining or losing weight, and whether the hair is showing a tendency to come out. In uraemia there may be a history of previous renal disease, but not uncommonly there is no such story and there may be delay in thinking of the cause of anaemia if routine blood urea examinations are not carried out.

BLEEDING DISORDERS

If a patient comes to the doctor because of haemorrhages into the skin or mucous membranes, or if he manifests a bleeding tendency in some other way, the chief possibilities to be considered are :—

Localised bleeding without any blood disorder being present: this is unlikely to cause skin haemorrhage, other than from trauma.

A coagulation defect, particularly haemophilia in the male: this does not cause purpura.

Thrombocytopenia, either idiopathic, or secondary to a variety of conditions, including leukaemia.

A capillary defect, including scurvy.

In questioning the patient it is important to ascertain whether there are numerous sites of bleeding and whether haemorrhage has occurred before and to enquire about the family history. It is unlikely, but possible, that a patient is bleeding because he is taking an anticoagulant drug.

As is well known, haemophilia is a condition that occurs in males, but the gene is carried by the female, and a similar pattern pertains to Christmas disease (factor IX deficiency). Other inherited bleeding disorders are less common.

It is not uncommon to find no previous family history of haemophilia in a patient with the disease. Indeed, in a survey of 54 haemophilic patients in the South East of Scotland, 17 had a history of the disease in previous generations, 16 had a history in the same or later generations, and 21 had no family history at all. A family history may be absent because

— the disease has been very mild in previous generations.

— there has been a genetic mutation.

Particularly if a bleeding tendency presents with purpura, it is important to enquire diligently about the taking of drugs, and to realise that these may cause purpura by damaging capillaries, causing platelet destruction or leading to marrow aplasia.

In difficult labours or certain operations, particularly on the lung, severe and possibly fatal bleeding may occur from fibrinogenopenia. A single laboratory test (Fibrindex) may give the diagnosis, but thereafter expert advice should be sought.

EXAMINATION OF THE PATIENT

General Appearance

The first thing to take account of is, of course, the patient's general condition with particular attention to pallor, dyspnoea, apparent weight loss, purpura and jaundice. Signs of myxoedema may be obvious.

As is well known, facial pallor is sometimes a misleading index of anaemia and one Registrar at the Blood Clinic in the Royal Infirmary was constantly being embarrassed by well meaning patients, who, having noted his naturally pallid appearance, suggested that he should have his blood examined. At least one of the patients who made the suggestion had rosy cheeks but a significant degree of anaemia, and looked much healthier than the Registrar. More valuable usually is examination of the conjunctivae and it is possible, with considerable practice, to estimate the haemoglobin level fairly exactly in this way in a high proportion of patients.

Signs of a bleeding tendency may consist of petechial haemorrhages, larger areas of ecchymoses, bleeding gums, swelling from haemorrhage into deeper tissues, or swelling of the joints.

Petechial haemorrhages occur in association with thrombocytopenia and are found particularly around the ankles. One female patient had the haemorrhages more on the face than elsewhere, but it transpired that she was performing as an acrobat in an Edinburgh theatre and that her partner was in the habit of holding her by the legs and whirling her round the stage. Petechiae may also be found in capillary purpura, including the drug induced forms, but in leukaemia or scurvy, larger bruised areas are likely. In haemophilia and Christmas disease, however, petechiae are not a feature, and it is probable that most haemorrhagic areas in these conditions are caused by trauma, including sudden muscle contractions, and that they seldom occur spontaneously. The two conditions, hereditary haemorrhagic telangiectasia and von Willebrand's disease, are rare hereditary bleeding disorders that need not be discussed further, but, in the former, telangiectasia (thin walled dilations of arterioles and capillaries) may be seen on the face, lips, mouth and perhaps conjunctivae as the patient becomes older, whereas in the latter condition the abnormal capillaries are not visible to the naked eye.

Jaundice is a typical sign of haemolytic anaemia, but is not always a feature and, as is well known, a lemon-yellow tint of the skin is said to be found in pernicious anaemia. It is only seen when the condition is advanced, and is usually difficult to identify with any degree of certainty. Nevertheless, it does occur sometimes and may assist the observer to make the correct diagnosis.

Various forms of rash other than petechiae occur rarely in acute leukaemia: such an eruption may be macular or papular. In chronic leukaemia there may be infiltration of the skin with the disease process. Again this is seen but seldom.

The Face and Neck

The experienced physician seeking clinical evidence of a blood disorder may quickly cast an eye over the general appearance of his patient, then look at the conjunctivae, the tongue and the finger nails, following this by examination of lymph glands, liver and spleen. Another method of approach is to work downwards, starting with an examination of the face, neck and mouth.

It is of value to note the hair, especially in the female patient, because myxoedema by itself or in conjunction with pernicious anaemia, may be the reason for a low haemoglobin level. If anaemia is severe there may be engorgement of neck veins, and in the routine examination the size of the thyroid gland should be noted and particular attention paid to lymph glands in the neck. It must be remembered that many normal persons have palpable glands in the cervical region, but that palpable supraclavicular glands are uncommon and that enlargement of the latter on the left side may be due to spread from a carcinoma of the stomach.

In examining the lymph glands of the neck it is important to palpate these systematically, including the ones below the jaw and at its angles, those along the jugular vessels, in the

posterior triangle, in front of and behind the ear, and in the supraclavicular areas. In a person who has had repeated sore throats, the glands at the angle of the jaw may be quite large, and in a thin but healthy person the glands in the neck may not only be palpable, but also visible. Students are frequently unaware of the extent to which lymph glands may be palpable in healthy persons. Almost everyone has palpable glands in the groin, and they are frequently to be felt in the axillae. It is unusual to be able to feel the epitrochlear gland in the upper arm.

If glands are felt in the neck and appear to be outwith normal limits of size, then consideration should be given to their number and to possible sources of infection such as the scalp. The examiner must note whether they are discrete, matted or fixed to the skin, and whether they are tender; he must also pay particular attention to their consistency. All this has to be done without alarming the patient who, nowadays, is liable to be well aware of the fact that enlarged glands are commonly found in leukaemia. In lymphadenoma the glands are rubbery and in malignancy they are harder. The possibility of tuberculosis must not be overlooked and here the glands may be matted and sometimes soft, but frequently they cannot be differentiated from those found in lymphadenoma. Lymph gland biopsy is commonly necessary if the diagnosis is not given by the blood or marrow findings.

The Mouth

In textbooks it is usually said that angular stomatitis is a sign of riboflavin deficiency, but in this country cracks at the angles of the mouth are more commonly attributable to iron deficiency. The gums are spongy and bleed easily in a patient with scurvy provided he is not edentulous, but gums that bleed when they are brushed are more commonly evidence of pyorrhoea. On the other hand, infected bleeding gums may occur in agranulocytosis, aplastic anaemia or leukaemia and, on occasion, a dentist who has suspected one of these conditions has referred the patient to the Blood Clinic. At this Clinic, too, are seen patients with glossitis and, as has already been said, this may indicate pernicious anaemia, folic acid deficiency, iron deficiency, depletion of riboflavin or nicotinic acid or sensitivity to the material of dentures. Occasionally a fungus infection may be responsible. It is very unusual, but not unknown, to find a furred tongue in pernicious anaemia. Usually if the tongue is dirty this diagnosis is incorrect. On the other hand, a truly inflamed tongue is found in only a small proportion of patients with the condition, and it is a most unusual feature of folic acid deficiency. It should be remembered that a very dry tongue may be an indication that a patient has uraemia, and this may be the cause of anaemia. A common cause of a dry tongue is that the patient sleeps with the mouth open, and a red tongue is sometimes due to the patient sucking "boilings". A very rare feature seen in the mouth is a blue line on the gums from lead poisoning, and this is a possible cause of anaemia.

One final sign in the mouth that should be mentioned is that in an early stage of infectious mononucleosis there may be haemorrhages at the junction of the hard and soft palate. Otherwise purpuric spots in the mouth usually have the same significance as those found in the skin.

The Heart and Lungs

As has already been said, pallor and dyspnoea may be a feature of hypertension, and it may also occur in aortic incompetence, whilst true anaemia is commonly a feature in subacute bacterial endocarditis. Anaemia of great severity or long duration is likely to be associated with cardiac failure and possibly anginal features, particularly if there is atheroma of the coronary vessels. There is an elevation of pulse pressure with an increased cardiac rate and output. There are systolic murmurs, and possibly basal crepitations. When cardiac failure with engorged neck veins and liver occurs as a result of anaemia, the patient's condition must be regarded as very serious, and if transfusion is decided upon it is advisable to use exchange transfusion.

In polycythaemia vera there is peripheral vasodilation and this diminishes the burden on the circulation. Vascular thromboses may occur.

The Abdomen

A careful examination of the abdomen is important in various forms of anaemia and in the reticuloses. Points to look for on visual examination are the colour of the skin, evidence of haemorrhages and the development of the circle of veins round the umbilicus (known as the caput medusae) that may be found in portal hypertension. This is due to blood flowing from the portal vein along a channel in the falciform ligament to the systemic system. A visible bulge is sometimes to be seen in the

abdomen if the liver or spleen is extremely large.

Palpation will include examination of glands in the groin and of the liver and spleen and a search for other palpable masses. It should be remembered that, as has already been said, most normal persons have palpable glands in the groin and in perhaps as many as 10% of persons the liver can be felt. On the other hand, if the spleen is palpable this is abnormal. The liver may be enlarged and firm in an anaemic person because of malignant disease (usually secondary), cirrhosis, chronic lymphatic or myeloid leukaemia, myelofibrosis, lymphadenoma, lymphosarcoma or certain other reticuloses.

None of these are very frequently encountered in this country, the commonest causes of a firm liver in association with anaemia probably being cirrhosis or malignancy. Other even rarer causes in Great Britain are amyloid disease, tuberculosis and malaria (this last if the patient has been in an infested area).

No doubt other articles in this series will deal with examination of the gastro-intestinal tract, but a point that should perhaps be made now is that if the liver is extremely large and hard, and if its palpation is commenced too high up in the abdomen, the edge may be missed and the inexperienced examiner may think that he is dealing with the board-like abdomen of an acute abdominal emergency such as a perforated duodenal ulcer. Sometimes, too, an enlarged gall-bladder or a carcinoma of the colon may be mistaken for an enlarged liver.

The causes of a very large spleen are chronic myeloid leukaemia and myelofibrosis, and it is in these two conditions that it may stretch beyond the umbilicus and be so hard that the careless examiner thinks he is dealing with a 'boarded' abdomen. The notch is not just a matter for academic discussion, but is usually a helpful feature of the examination. When the spleen is very large it may be important to decide whether the liver is also enlarged, and sometimes when both organs are massive an apparent notch is felt where the liver and spleen meet. Moderate splenic enlargement is found in chronic lymphatic leukaemia, lymphadenoma, lymphosarcoma and certain rare forms of reticulosis and in portal hypertension, glandular fever and haemolytic anaemia. The spleen may be felt in iron deficiency anaemia or pernicious anaemia, but palpable enlargement is rare in these, particularly in the latter. The possibility of malaria must be remembered if the patient has visited the tropics. If a patient is believed to have idiopathic thrombocytopenic purpura and the spleen can be felt, the diagnosis is probably wrong.

It is important to remember that an enlarged kidney may be mistaken for an enlarged spleen. The fingers can usually be pushed deep to the anterior edge of the spleen, but this manoeuvre cannot be done in relation to the kidney, whilst with the former organ the fingers cannot be pushed between the mass and the costal margin. The edge of the spleen is always smooth and rounded, but it is frequently impossible to feel the enlargement unless the patient is lying flat and at ease, with the knees partially bent. Even then the fingers must be dipped at the height of inspiration.

Other palpable abnormalities that may be associated with anaemia are carcinomatous masses in the caecum, colon or stomach, fibroids of the uterus and, rarely, carcinoma of the kidney. This last must be remembered as a possible symptomless cause of undiagnosed fever, sometimes with anaemia.

It should always be remembered that a palpable mass in the lower abdomen of a female patient may be gravid uterus and that fibroids can be very large and hard.

Percussion

The main value of percussion is to confirm the enlargement of the liver or spleen.

Very rarely in polycythaemia, hepatic vein thrombosis will cause ascites.

Rectal Examination

If the reason for iron deficiency is not evident, proctoscopy and rectal examination will be required. It must be remembered that haemorrhoids cannot be felt unless they are inflamed.

Nervous System

Vibration sense is tested by applying a tuning fork vibrating at 256 cycles per second to bony prominences, and in anaemia the sensation may be lost in the distal part of the lower limbs. If, however, the loss is extensive, extending to the iliac crests, this is usually taken to indicate damage to the posterior columns of the spinal cord, a complication of pernicious anaemia or, more rarely, of vitamin B_{12} deficiency from some other cause. It does not occur in folic acid depletion or other forms of anaemia. It is relatively uncommon nowadays, because of earlier diagnosis, for degeneration to occur in both the posterior and lateral columns in pernicious anaemia (subacute com-

bined degeneration of the cord), but it can occur, particularly if the condition is of long duration, if folic acid therapy has been given alone or if the patient is a very rigid vegetarian (Vegan) who thus obtains folic acid in the diet without adequate vitamin B_{12}. Sometimes the neurological features occur without anaemia. In postero-lateral degeneration there may be extensor plantar reflexes and increased or diminished knee and ankle jerks, with loss of vibration sense.

The patient with severe anaemia is forgetful and unable to concentrate, and in megaloblastic anaemia there may be dementia.

Examination of the retinae is of interest in patients with severe anaemia, but is seldom of diagnostic value. There may be pallor of the disc and the rest of the fundus, the retinal vessels being pale and tortuous. Retinal haemorrhages and blurring of the disc margins may occur in any severe anaemia, and in acute leukaemia there may be extensive haemorrhages and exudates, venous engorgement and fundal oedema.

Locomotor System

The spoonshaped nails of iron deficiency (koilonychia) are seldom seen, but some flattening is common in this condition. If an anaemic person has clubbing of the fingers, this suggests chronic infection, particularly of the chest, or possibly a malabsorptive disorder or intestinal carcinoma. There may be clubbing together with secondary polycythaemia in congenital heart disease or chronic chest disease. Vague aches and pains in the limbs generally, or in the region of the joints, may be the presenting feature in acute leukaemia. The patient with haemophilia or Christmas disease may attend the doctor or hospital clinic with joint swellings and there may be considerable difficulty about diagnosis if he does not tell the doctor that he is a 'bleeder'. Occasionally a patient with haemophilia omits to do this because he does not think of the condition, about which he usually knows so much, as an illness.

The presence of oedema indicates that anaemia is severe, or, rarely, that enlarged glands are causing obstruction.

Bone tenderness, particularly of ribs or sternum, may be a feature of leukaemia or myelomatosis.

The second part of this article, which continues the series on the examination of the various systems, will be printed in the next number of RES MEDICA.