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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
Much has been said in the first part of this article about the important points to note in taking the history, and various possible physical signs have been considered. In many instances, however, further investigations are necessary before a diagnosis can be made or confirmed. These cannot be considered in great detail in an article of this nature, since complete consideration would involve writing a full textbook of haematology, but some of the more important investigations can be outlined under three headings according to the degree of complexity or specialisation.

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THE INVESTIGATION OF A PATIENT BELIEVED TO HAVE A BLOOD DISORDER

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

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FURTHER INVESTIGATIONS

Much has been said in the first part of this article about the important points to note in taking the history, and various possible physical signs have been considered. In many instances, however, further investigations are necessary before a diagnosis can be made or confirmed. These cannot be considered in great detail in an article of this nature, since complete consideration would involve writing a full textbook of haematology, but some of the more important investigations can be outlined under three headings according to the degree of complexity or specialisation.

Simple Laboratory Investigations

Blood counts. The routine investigation of a patient with a suspected blood disorder includes estimation of the haemoglobin level and the white cell count, together with examination of a blood film. These can be done from finger prick blood. Many haematologists are unwilling to perform erythrocyte counts on the grounds that they are so inaccurate as to be positively misleading, but with modern electronic counters this is not the case.

If the patient is anaemic, it is desirable to know the mean corpuscular haemoglobin concentration (MCHC) and mean corpuscular volume (MCV), and although there are micro methods available, it is better to have a sample of venous blood for the haematocrit reading. The study of a stained blood film by an experienced observer is essential, and a differential white cell count and E.S.R. may be necessary. If there is any question of thrombocytopenia a platelet count will be required, but this can be preceded by inspecting a blood film stained with cresyl blue as this will show whether or not platelets are present. The more usual use of cresyl blue staining, frequently together with a Romanowsky stain such as that of Leishman, is to enable a reticulocyte count to be done, and this is of particular value in haemolytic anaemia, in continued bleeding, or in assessing response to therapy.

Other simple tests include:—

(a) The bleeding and coagulation times: the former is prolonged in thrombocytopenic purpura and the latter usually (but not always) in haemophilia and Christmas disease.

(b) Testing the urine for excess of urobilinogen with Ehrlich's aldehyde reagent: this is positive in haemolytic anaemia and in untreated pernicious anaemia, but, of course, there are numerous other causes for urobilinogenuria.

(c) An augmented histamine test of gastric acid secretion. This is an essential investigation in suspected pernicious anaemia,

but the administration of a large dose of histamine, even when covered by an antihistamine drug, may give troublesome side effects and the test should not be done in untreated severe anaemia. A new method involving the use of pentagastrin as a gastric acid secretory stimulant is being investigated.

(d) Bone marrow aspiration. This is probably done more often than is really required, but if a patient with a blood disorder is treated without marrow puncture being performed, and the first diagnosis is incorrect, this valuable method of investigation may have been eliminated by treatment. Sometimes there is considerable difficulty in obtaining marrow from the sternum, and a small trephine may have to be used to obtain a sample from the iliac crest.

Sometimes valuable information is obtained from the "buffy coat" of the peripheral blood.

(e) Tests for blood in the faeces. Repeated tests are an essential part of the investigation of iron deficiency anaemia where the cause of the condition is not clear. The relative values of the various methods need not be discussed here, but it should be noted that the name Ham's reagent is applied by different authorities to two different reagents used to test faeces for blood.

(f) Sigmoidoscopy. This may be an essential investigation in iron deficiency.

(g) Barium enema, meal and follow through. The cause of iron deficiency anaemia or of megaloblastic anaemia associated with malabsorption may not be clear until full barium studies have been done. In iron deficiency the disorders being sought include not only carcinoma, but also diaphragmatic hernia and oesophageal varices.

(h) Blood grouping.

More Complex Investigations

The student who does not know of any of these tests and wishes to do so should consult a suitable textbook. Those that are most commonly employed are as follows:—

1. In suspected or known megaloblastic anaemia.
   (a) Serum vitamin B_{12} and folate estimations.
   (b) The Schilling test or other test of the absorption of labelled cyanocobalamin.
   (c) Repetition of this test with the administration of intrinsic factor or after giving tetracycline to eliminate organisms in blind loops.
   (d) Jejunal biopsy.
   (e) FIGLU tests. These are of little value, except perhaps when there is malabsorption of folic acid.
   (f) Folic acid absorption tests.
2. In hypochromic anaemia.
   (a) Blood urea estimation (uraemia may be overlooked).
   (b) A search for chronic infection.
   (c) Gynaecological examination.
   (d) A search for malignancy, e.g. of the kidney.
   (e) A dietetic history.
   (f) Estimation of serum iron and iron binding capacity.
3. In bleeding disorders.
   (a) Platelet count.
   (b) Capillary resistance test.
4. In haemolytic anaemia.
   (a) Red cell survival studies, using ^{51}Chromium labelled red cells.
   (b) Coombs' test (direct and indirect antiglobulin reaction).
   (c) Tests for haptoglobins.
   (d) Osmotic fragility.
5. Miscellaneous.
   (a) Tests of thyroid function.
   (b) Estimations of red cell volume (e.g. by ^{51}Cr) or plasma volume (e.g. by ^{125}I labelled human serum albumin).
   (c) The Paul-Bunnell test is usually positive in infectious mononucleosis after the first week, but there have been reports of it being negative, especially in epidemics.

Specialised Tests

1. Red cell folate estimations — this probably gives a better indication of folate stores than does serum folate estimation.
2. ^{59}Fe clearance studies from plasma. This is related to marrow activity.
3. ^{59}Fe turnover studies. In normal subjects 70 to 80 per cent of the iron is incorporated into the red cells by 14 days.
4. Tests of splenic uptake of ^{51}Chromium labelled red cells, and comparison with counts over the heart and liver.

5. Use of ^{51}Cr labelled red cells to demonstrate gastro-intestinal bleeding.
6. Parietal cell antibodies.
7. Intrinsic factor assays.
8. Thromboplastin generation tests.
9. Measurement of Antihaemophilic factor level in blood.
10. Iron absorption tests using a whole body counter and ^{59}Fe.
11. Vitamin B_{12} absorption tests using cobalt-labelled vitamin B_{12} and a whole body counter.
12. Tests for haemoglobinopathies.
13. Marrow culture for tuberculosis.
14. Chromosome studies in suspected chronic myeloid leukaemia.
15. Further complex tests for immune antibodies.
16. Acidified serum test (Ham's) for paroxysmal nocturnal haemoglobinuria.
17. Brilliant cresyl blue decolourization or methaemoglobin-reduction tests for glucose-6-phosphate deficiency.

This list, which is incomplete, indicates the complexity of the investigations that may be required in the more obscure blood disorders and the way in which diagnosis may be far removed from simple history taking and clinical examination. Fortunately, such complex investigations are but rarely required but when they are, they have to be done in very specialised laboratories.

ERRORS OF DIAGNOSIS

It is sometimes of particular value to be reminded of possible errors of diagnosis and to learn of the mistakes of others. Curiosities, errors and tragedies that the writer has encountered include the following:—

Three sisters became anaemic. All had pernicious anaemia.

A patient with pernicious anaemia was put on a waiting list for admission to hospital, but died, untreated, before she was sent for. It should be remembered that although the condition is usually slow of onset, there may be sudden rapid deterioration.

The sister of a male patient with pernicious anaemia was admitted to a mental hospital and died. Nobody had thought of the possibility of the condition being familial or of the mental disturbance being due to vitamin B_{12} deficiency, but the cause of death was pernicious anaemia. (This was outwith the Edinburgh area).

A patient with anaemia, leucopenia, thrombocytopenia and purpura was thought to have aplastic anaemia because of these features and the fact that marrow was not obtained on sternal puncture. Fortunately, the serum vitamin B_{12} level was estimated and gave the correct diagnosis, viz. pernicious anaemia.

A female patient with menorrhagia had severe anaemia with a colour index of 0.4 and an MCHC of 22. She had pernicious anaemia and severe iron deficiency.

A female patient with bronchial asthma who had been under treatment for a very long time with prednisone, became weak, tired and apathetic. There was mild anaemia and a normoblastic marrow. She, too, had pernicious anaemia, but the marrow picture had been obscured by steroid therapy.

A patient with congenital haemolytic anaemia became very much more anaemic in pregnancy. She had developed megaloblastic anaemia from folic acid depletion.

A pregnant woman who developed severe megaloblastic anaemia was, in fact, not suffering from megaloblastic anaemia of pregnancy alone, but from gluten enteropathy with severe malabsorption of folic acid and vitamin B_{12}.

A patient who had served in the Army in India was admitted to hospital with anaemia, leucopenia, and a large spleen. He had kala azar.

A youth who had recently been in West Africa had mild anaemia and attacks of shivering and weeping, but no significant fever. He had cerebral malaria.

A patient had fever and thrombocytopenia. No cause could be found, but eventually the patient was found to have a malignant tumour of the thymus.

A patient had purpura and slight fever. The cause was chronic meningococcal septicaemia.

The parents of a child who recovered from leukaemia were anxious to have the occurrence officially accepted as a miracle. The blood film was one of glandular fever.

A patient who had been diagnosed as having leukaemia did not deteriorate as he and his family expected. The blood film showed myelocytes and the spleen was very large, but the diagnosis (incorrectly made outwith Scotland) was myelofibrosis.

The parents of a child were incorrectly told that he was suffering from leukaemia because the observer did not realise that there is sometimes a focus of lymphocytes in a normal marrow.

A patient with anaemia, leucopenia and

thrombocytopenia was found to have a hyperplastic marrow on sternal puncture. She died and it was found that almost all the marrow was aplastic, but the marrow puncture needle had not struck a representative area.

The Vice-President of a very major American corporation was admitted to hospital suffering from acute leukaemia and was about to be treated for this when the intern pointed out to the consultant that the patient might be having a leukaemoid reaction to tuberculosis, and suggested that the chest should be X-rayed. The intern's suggested diagnosis was the correct one!

A patient who had had a partial gastrectomy many years before was sent to an outpatient department because of paraesthesiae and peculiar impairment of sensation in the limbs. His doctor thought he might have subacute combined degeneration of the cord. The patient was asked whether he had ever taken thalidomide. At first he denied this, but finally admitted that it had been prescribed for his wife but he had taken it. When thalidomide was in use it caused impairment of sensation in the limbs in a number of patients. This drug is not now used, but in considering a possible iatrogenic disease it is important to remember that a patient may be taking medicines prescribed for a relative.

A patient who had been under treatment in hospital for two days for rheumatic fever was recognised by a physiotherapist as a haemophiliac who was known to her. Neither the patient nor his doctor had mentioned that he had haemophilia, and the joint swellings due to bleeding were thought to be due to acute rheumatism.

A patient who was under observation for idiopathic thrombocytopenic purpura developed extensor plantar responses, and a splenectomy was done immediately as this was thought to be because of an upper motor neurone lesion due to haemorrhage. In fact, she had developed disseminated sclerosis in addition to her thrombocytopenic purpura.

These examples are given as they may be of interest and because it is hoped that they may lead to avoidance of similar mistakes in the future. The student should not, however, be too depressed about the possibility of making a correct diagnosis in a patient with a blood disorder. In the great majority of instances the patient is a female suffering from iron deficiency anaemia, and the reason is that the loss exceeds the intake.