Diagnosis and Treatment of Blood Diseases

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INTRODUCTION

THE book is designed for the practising physicians and post-graduate students who wish to be able to diagnose and treat their patients suffering from blood diseases by utilising present-day diagnostic techniques and therapeutic methods. The standard textbooks of hæmatology have become very large since they have to take notice of the considerable new fundamental knowledge of the structure and properties of blood cells and of what is briefly known as "erythrokinetics", and of experimental work on the nature of diseases like leukæmia. It is not easy for those who have neither the time nor the inclination to study all this material to find their way to the parts of the book that they need for day-to-day guidance in the management of patients with blood diseases. There are available excellent handbooks describing the laboratory techniques needed for hæmatological studies; but again these are designed mainly for another group—the pathologists who carry out and supervise these investigations, and so they contain considerable detail which the physician does not need and the lists of "significance" of the various test results which, while comprehensive, may also be confusing.

The present book, therefore, concentrates on the problems of diagnosis and treatment as they present themselves to the physician. But anyone who undertakes this task seriously must be prepared to carry out some of the laboratory procedures for himself, especially in doubtful cases, and he must be familiar with the principles and minimum details of the important laboratory methods so that he can understand their limitations as well as their significance. Every cardiologist interprets his own electrocardiograms and prefers to carry out his own X-ray screening; no orthopædic surgeon would base treatment on someone else's report on the radiograms. In the same way the physician dealing with blood diseases should be able to study and form his own opinion about the appearance of blood and bone-marrow cells, spleen puncture material, and, if possible, histological material from lymph glands, spleen, marrow and other organs likely to be affected in blood diseases.

For these reasons the book begins with a section on the clinical examination of the patient with suspected blood disease, followed by one on laboratory methods in which the most useful techniques are briefly described and their significance discussed. Methods for the investigation of particular groups of diseases are discussed in the

chapters dealing with these diseases; e.g. blood clotting methods are discussed in the chapter on hæmorrhagic diseases. Details of techniques used by the author are given in Chapter 18, but those who need fuller information are referred to standard texts like Dacie's *Practical Hæmatology*. The author has fully described and illustrated in colour the appearances of all bone-marrow and most of the blood cells in his *Atlas of Bone-Marrow Pathology* and the reader is intended to use this for illustration and for assistance in studying blood and marrow films.

References are not often included in the text, but a short list of general reviews and key papers is given at the end of each chapter.

M. C. G. I.

CONTENTS

Chapter 1

CLINICAL DIAGNOSTIC METHODS

In the diagnosis of blood disease it is just as important to take a proper history and carry out a full clinical examination as in any other division of medicine. Many anæmias are secondary and the clue to the cause may be found at this first examination. The history and clinical examination should indicate the first lines of investigation and help the speed of diagnosis.

History. There are some special points that should be enquired about when a blood disease is suspected. For instance, the occurrence of sore tongue, flatulent indigestion, bowel activity, the frequency and amount of menstrual loss, any skin rash, repeated bleeding from the nose or other mucous membranes, any history of visual disturbances, any œdema especially of ankles. The previous medical history can be important, especially if any alimentary-tract operations have been carried out. Family history is of importance in the hæmorrhagic diseases, in hæmolytic anæmias and some other diseases. It is very important to enquire about previous treatment, because this can significantly alter the clinical picture sometimes within 48 hours. Clinical examination must be thorough. A pale face with or without icterus suggests anæmia, but it is better to look at the conjunctivæ and their colour gives a clue to the severity of any anæmia and the degree of urgency in dealing with the patient. The general nutrition should be assessed and any wasting noted. The pulse rate is usually rapid and dropped beats due to extra systoles are not uncommon; other irregularities call for cardiological investigation. When the *pulse* is taken, the nails are inspected especially for the koilonychia of iron-deficiency. The *skin* is inspected for petechiæ, purpura, or any unusual pigmentation or infiltration. *The heart* is affected only if the anæmia is severe; then enlargement may occur. Hæmic murmurs are usually soft, systolic and maximal at the base, but in severe anæmia, especially pernicious anæmia, almost any valvular murmur can be mimicked and will disappear when the anæmia is relieved. Anæmia can sometimes be the presenting sign of sub-acute bacterial endocarditis. *Blood pressure* is commonly lowered in anæmia; a high reading indicates that investigation of renal function, particularly estimation of blood urea, is needed. In the *lungs* basal râles due to œdema and other

signs may be found; if any suspicious sounds are detected at the clinical examination, a radiogram is indicated so that any lesion like leukæmic infiltration or enlargement of mediastinal glands can be precisely delineated. Anæmia can be secondary to pulmonary tuberculosis and bronchial carcinoma.

Examination of the *abdomen* is, of course, most important. Enlargement of the spleen or the liver is detected and the degree recorded. Any abnormal abdominal mass may suggest alimentary tract malignancy, enlarged abdominal lymph glands, or other tumours known to produce anæmia which may thus be the presenting sign.

Lymph Gland sites should always be examined, the neck, axillæ and groins being the most important. Lymph gland enlargement is particularly significant in blood diseases and if found it is important to enquire how long the swelling has been present and if it varies in size.

The central nervous system does not often have to be examined in great detail. The reflexes and the plantar responses should be elicited, pupil reactions tested and the fundi examined with an opththalmoscope. If the patient complains of sensory disturbance, this function should be tested too. The presence or absence of *œdema* especially of ankles and feet should be checked.

Urine examination is part of the clinical test and, if necessary, deposit is examined microscopically for the presence of red cells, pus cells, or casts. Rectal and sometimes vaginal examination is needed if the history suggests a lesion in these areas.

Chapter 2

LABORATORY INVESTIGATIONS

LABORATORY investigation is needed for every patient suspected of having a blood disease. The investigations needed for most patients are described here and their value and significance discussed; technical details of recommended methods are given in Chapter 18. Special tests used in particular conditions are described in the chapters dealing with these diseases.

Red Blood-cell Counts. The usual method is to use a hæmocytometer; most workers today prefer the "improved Neubauer" rulings and use a double chamber for duplicate counts. Red-cell counting by this method has been much criticised by the statistically-minded because of the large range of possible variation. In some laboratories red-cell counts are not carried out; instead the mean corpuscular hæmoglobin is estimated and the stained film examined. This method works well enough with iron-deficiency anæmias, but is liable to miss the earlier macrocytic anæmias and polycythæmias; e.g. the patient who has 75 per cent hæmoglobin but only 3,000,000 red cells p.c.mm., or 90 per cent hæmoglobin but 7,000,000 red cells p.c.mm. For these reasons red-cell counts have always been carried out in our department; with Dacie's techniques that avoid the use of bulb pipettes, a trained technician obtains surprisingly consistent results.

Lately electronic cell-counting machines have been introduced. One of them, the EEL, has now been in regular use in Manchester for some time. It enables four counts to be made and averaged in one minute. When working properly it is very efficient and has considerably speeded the work. Other machines, some simpler than the EEL, are being introduced and there is no doubt that cell-counting by machine will replace counting by technician in all departments that have enough work to justify the purchase and maintenance of a machine costing £600 to £1,000. Normal range, 4,800,000–5,500,000 p.c.mm. for males; 4,500,000–5,200,000 for females. This and other normal ranges are not so wide as those given in some textbooks; they have been chosen with clinical significance in mind, and figures outside the ranges given here should suggest to the physician that they *may* be abnormal.

White-cell counts and *platelet* counts are still carried out by technicians for the most part; machine counting is being developed but is

not yet in general use. For white-cell counts Dacie's technique is used; normal adult range, 4,000–10,000 p.c.mm. For platelet counts Lempert's technique is preferred giving a normal figure of 250,000 p.c.mm. Details are given in Chapter 18.

Reticulocyte counts are needed in patients with hæmolytic anæmia and in checking the response to treatment of patients with megaloblastic anæmias and severe iron-deficiency anæmia. Normally reticulocytes do not exceed 2 per cent even in very anæmic patients. Supravital staining with brilliant cresyl-blue is used.

The differential white-cell count is of great importance. Thin, uniformly made blood-smears are essential; staining with the Jenner-Giemsa combination using a buffer solution to obtain uniform results is the best method. At least 250 cells are counted. Nothing is to be gained from elaborate methods of sampling the whole surface. Normal figures: polymorphonuclears 40–75 per cent, lymphocytes 20–40 per cent, monocytes 2–10 per cent, eosinophils 1–6 per cent, basophils 0–1 per cent. Only gross variations from these ranges are really significant.

Some special staining methods are used for leucocytes. The oxidase and peroxidase methods give little help, but methods for detecting alkaline phosphatase activity in granulocytes have proved helpful and a suitable technique is given in Chapter 18.

Hæmoglobin. Most laboratories now use photo-electric colorimeters specially designed for hæmoglobin estimation. If such an instrument is not available the Haldane carboxyhæmoglobin method which now has a British Standard Specification or the Medical Research Council's grey-wedge photometer are recommended. The present standard takes 14·6 g. Hb/100 ml. as 100 per cent. Normal ranges: males, 14·0–16·0 g./100 ml. (96–110 per cent); females, 13·2–15·2 g./100 ml. (90–104 per cent).

Packed Cell Volume (P.C.V.). The standard technique uses Wintrobe tubes, but lately a micro method has been introduced. This uses capillary tubes treated beforehand with heparin; the tubes are filled from finger-prick blood, sealed and then centrifuged in special holders. This method has proved reasonably reliable and is being widely adopted. The P.C.V. is specially useful for calculating the *mean corpuscular hæmoglobin concentration* (*M.C.H.C.*) which is the value of Hb in g./100 ml. blood/P.C.V. $\times$ 100. The normal range is 32–36 per cent and figures *below* this range indicate iron-deficiency anæmia. In megaloblastic anæmias the M.C.H.C. remains within the normal range.

Bone-marrow Examination. This is now an essential part of all but the simplest cases of suspected blood disease. The peripheral blood picture is usually sufficiently diagnostic in iron-deficiency anæmia in women and in conditions like chronic lymphatic leukæmia which have a very characteristic blood picture. In all other cases bone-marrow

examination should be carried out as part of the initial investigation, and *it is absolutely essential that no treatment, other than iron, should be given beforehand.* Folic acid, vitamin B_{12}, liver extracts, stomach-mucosa preparations can all alter the bone-marrow picture so that, within 24 hours, a completely misleading picture will be found. If the patient has received any of these substances, it is necessary that the fact should be known to whoever examines the marrow smears. Techniques for examination of the marrow are now well established and are given in Chapter 18. Full descriptions of the cells found are given and illustrated in the *Atlas of Bone Marrow Pathology* (Israëls, 1955) ; plates showing typical marrow pictures in various conditions are reproduced in this volume and normal marrow pictures are shown on Plate 1, Figs. 1 and 2.

Bone marrow examination gives positive *diagnostic* information in the following conditions:

1. *Pernicious anæmia; the megaloblastic anæmias* in steatorrhœa, pregnancy, infancy and nutritional deficiency and that which sometimes occurs in patients receiving anti-convulsant drugs such as phenytoin and primidone. The bone-marrow picture will *not* show whether the megaloblastic anæmia is due to vitamin B_{12} or folic acid deficiency.
2. *Aleukæmic Leukæmia.* By this is meant a leukæmia in which abnormal cells are absent or too few for diagnosis in the peripheral blood.
3. *Myelomatosis* in which the marrow shows a very typical infiltration with plasma cells often of abnormal appearance.
4. *Reticulosis and reticulo-sarcoma* in which groups of abnormal cells in the marrow may indicate the diagnosis before more definite signs, like enlarged lymph glands, have appeared.
5. *Gaucher's disease* and other lipoidoses.

Important though not diagnostic information is obtained in the following group of conditions:

6. *Macrocytic* (*High Colour-Index*) *Anæmia.* In addition to the megaloblastic anæmias, macrocytic pictures can occur in hæmolytic anæmias, aplastic types of anæmia due to various causes, and in leukæmias especially of the acute varieties. The marrow picture will show to which of these groups a case belongs.
7. *Purpura and hæmorrhagic diseases associated with a low platelet count.* Marrow examination helps to distinguish between primary and secondary thrombocytopenia; the secondary form is often due to leukæmia or to aplastic anæmia which have characteristic marrow pictures.
8. *Malignancy.* Occasionally secondary malignant cells found in bone marrow smears are the first clue to the cause of a patient's anæmia.

Spleen Puncture. This is a simple and safe procedure that has proved helpful in the diagnosis of splenomegaly. The technique is similar to that of Moeschlin (1957) who has written a comprehensive monograph on this subject. The needle is a long thin one, we actually use a Gentille lumbar puncture needle provided with a suitable guard. The site of the puncture is best 3–5 cm. below the costal margin near and posterior to the anterior axillary line. This is suitable for the enlarged spleen that is easily palpable when the patient inspires deeply; we prefer not to attempt the puncture of spleens that are less enlarged. After suitable local anæsthesia the needle is pushed through the abdominal wall until the surface of the spleen can just be felt. The stilette is withdrawn and a 20 ml. syringe fitted. The patient is then instructed to take a deep inspiration and then to *hold his breath*. When he does this the needle is pushed rapidly about 2 cm. into the spleen, the syringe piston is withdrawn to the *full extent* and held there for a few seconds, then the piston is gently released and the needle withdrawn. It is very important that the suction should have ceased before the needle is withdrawn. A few drops of fluid are obtained; the material is gently blown out on to glass slides and smears are made at once. They are stained with Jenner-Giemsa in the usual way. Before carrying out the spleen puncture, platelet count and prothrombin estimation should be checked; the platelet count should be at least 40,000 p.c.mm., and the prothrombin not below 50 per cent.

Moeschlin states that in the normal spleen smear 60–80 per cent of the cells are lymphocytes, mostly small, and the rest are mostly neutrophil polymorphs. A few serosa cells, plasma and reticulum cells, and one or two normoblasts are the only other cells present. In certain diseases the picture seen on examination of the smear is grossly different from normal, and it is only gross differences that are significant. In *myelosclerosis*, hæmopoiesis starts again in the spleen and the picture looks more like a hyperplastic marrow smear; normoblasts, proerythroblasts, granulocytes of all types and stages and megakaryocytes are present, lymphocytes are not more than 20 per cent. In *myeloid leukæmia* granulocytes of all stages with a few normoblasts have displaced most of the lymphocytes, but megakaryocytes are unusual.

Reticuloses responsible for splenic enlargement have sometimes been diagnosed by spleen puncture when abnormal or primitive reticulum-cell types have been found in fair numbers; sometimes the very typical reticulo-sarcoma cells have given the clue to the diagnosis.

Blood grouping and allied tests like the Coombs reaction to test the presence of antibodies on the surface of red blood-cells are an important part of the investigation of many patients with blood diseases. The actual techniques are best left in expert hands, for reasons of safety; but anyone who wishes to know more has many books to choose from: *Basic Essentials of Blood Group Theory and Practice*, by K. E. Boorman and B. E. Dodd (1961), can be specially recommended.

Investigations for testing *Blood Clotting* functions are described in Chapter 7 in the hæmorrhagic disorders.

This list of investigations is a long one and, in addition, there are special diagnostic tests employed when certain groups of diseases are suspected. The *minimum* investigation for every patient thought to have a blood disease should comprise a red-cell count, a white-cell count, estimation of hæmoglobin content of the blood and a differential white-cell count together with a scrutiny of the stained smear for any structural red-cell abnormalities and presence of blood platelets. Other tests employed will depend on the differential diagnosis reached after history taking and clinical examination.

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Boorman, K. E., Dodd, B. E. (1961), *Basic Essentials of Blood Group Theory and Practice*, Churchill, London.

Dacie, J. V. (1956), *Practical Hæmatology*, 2nd edition, Churchill, London.

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Chapter 3

IRON-DEFICIENCY ANÆMIA

THE total iron in the body has been estimated to be between 4 and 5 grams. The regular loss is small; for adult males the figure is 0·5 to 1·5 mg. daily mainly in urine, sweat and by desquamation of skin, for adult females the figure is 1·0 to 2·5 mg. daily during reproductive life because 10 to 40 mg. are lost at each menstrual period. During pregnancy, even allowing for the amenorrhœa, some 400–500 mg. of iron is needed for the infant and for losses at birth, so that 2·0 to 2·5 mg. daily are needed on the average. European and North American diets provide about 12 to 15 mg. daily of which 0·6 to 1·5 mg. is absorbed.

These figures show that most persons have no shortage of iron, but in females in the reproductive period of life and during pregnancy the iron balance, even with an adequate diet, is precarious. It is not surprising that iron-deficiency anæmia is the commonest of all anæmias among women between the ages of 18 and 50, and it is indeed one of the commonest conditions that the general practitioner sees.

The clinical picture is classically one of insidiously increasing pallor without icterus, dyspnœa and palpitation on exertion, some œdema of the ankles towards the end of the day, and increasing fatigue after effort previously well within the patient's capacity. Occasionally, especially in the older patients, angina of effort may be the main symptom. Soreness of the tongue, indigestion, brittle nails are sometimes the cause of complaint. On examination the patient is pale with minimal icterus. The pulse rate is rapid. The nails may show the typical koilonychia. The tongue may be smooth and sometimes red and moist. A few patients complain of increasingly severe dysphagia. The spleen may be palpable but is rarely much enlarged. The other signs are those of anæmia in general, but however obvious the anæmia a thorough physical examination of all systems is essential since the cause of the anæmia may be revealed; a tumour may be palpated in the abdomen or the pelvis, signs suggestive of a lung affection may be found, for example.

Laboratory Tests

The red-cell count is rarely below 3 million per c.mm., but the *hæmoglobin* is proportionately much lower so that the *colour index* is less than one, often 0·5 to 0·7.

The M.C.H.C. is always lower than the normal 32 per cent. The *white-cell* count is typically low or normal; a count over 10,000 p.c.mm. suggests that the anæmia is secondary, e.g. to malignancy or infection. The *stained blood film* shows typical small *red-cells* with pale centres, a few quite regular target-cells are often found. The differential white-cell count should be normal, the platelet count normal and reticulocytes low.

The bone-marrow shows changes in cellularity that vary with the cause. If blood loss is responsible for the anæmia the marrow will be very cellular with a considerable increase of erythroblasts; if the cause is defective nutrition, the marrow may well be less cellular than normal. All cases, however, show characteristic changes in the erythroblasts. Normoblasts of all stages from early to late are present together with some pro-erythroblasts; all these cells tend to be smaller than normal, in particular the intermediate normoblasts show small and densely-staining nuclei with scanty or ragged grey-blue cytoplasm. The granulocytes often show this shrinking as well and many of the cells are small and stain densely. Megakaryocytes, plasma cells and lymphocytes can usually be found. No abnormal cells should be present. Marrow pictures are shown on Plate 2, Figs. 3 and 4.

Special Tests

1. It is often helpful to *stain the marrow for iron:* if the iron stores are depleted, very little stainable material will be present.

2. *Serum iron* estimation is not easy owing to the low normal figure, 75–175 μg./100 ml. In iron-deficiency anæmia the figure is usually below 40 μg./100 ml., but in mild cases figures within the normal range may be found.

3. *The unsaturated iron-binding capacity* of plasma is a measure of the amount of iron that the plasma is still capable of taking up; the normal range is 150–300 μg./100 ml.; in iron-deficiency anæmia the figure is increased to 300–750 μg./100 ml. The value of this determination is that it distinguishes iron-deficiency anæmia from other anæmias in which the plasma or serum iron is low; for example, in the anæmias found in some patients with rheumatoid arthritis, chronic infections, and some malignant conditions not associated with blood loss, low serum iron levels are frequent, but the iron-binding capacity is normal.

MANAGEMENT

Once the presence of iron-deficiency is established, the management of the patient and the amount of investigation to be undertaken depend on the severity of the anæmia and on the age of the patient. John Fry (1961) in his valuable survey of the incidence of anæmia in general practice pointed out that iron-deficiency accounted for 92 per cent of all his cases, and that in 83 per cent of the *female* iron-deficiency patients no serious underlying disease was found. These women were

mostly in the reproductive period of life when, as we have seen, iron balance is often not well maintained. A practical management scheme can, therefore, be based on age and sex.

Women in the reproductive period of life can safely be treated with a simple oral iron preparation for one month. If there is no response, or the response is poor, further investigations must be undertaken; Fry's figures show that in practice only 1 in 10 of such patients will need this further study.

Women Past the Menopause. Many of these patients too have simple iron-deficiency, but any physical signs suggestive of malignancy, the presence of a polymorphonuclear leucocytosis, or a hæmoglobin level of under 6 g./100 ml. are warnings that investigations should proceed without delay.

Males of all Ages and Girls under 15 Years. Primary iron-deficiency anæmia does occur in both these groups, but is uncommon. A source of blood loss should be looked for in the males especially peptic ulcer, or bleeding piles; in the girls, underlying steatorrhœa is sometimes found.

The further investigation that is required for patients who do not respond to simple iron treatment can be divided into:

1. A search for sources of blood loss.
2. A search for conditions causing malabsorption of iron.
3. Enquiries about possible dietary deficiencies.

1. Sources of Blood Loss. A. From the Alimentary Tract

Here examination of the stools for the presence of occult blood is essential, since persistently positive tests are valuable evidence that the source of blood loss is in the alimentary tract. The commonest conditions that are associated with iron-deficiency anæmia are as follows:

Piles: a history of fresh blood passed with motions and pain on defæcation can often be obtained by questioning; inspection with or without proctoscopy should show the presence of hæmorrhoids.

Peptic ulcer: the characteristic history may be missing, but a barium meal should be carried out in all cases. In young patients a peptic ulcer inside a Meckel's diverticulum may be a puzzling source of blood loss; the diverticulum can sometimes be shown by barium radiography, especially if its presence is suspected.

Carcinoma of the stomach and the colon: the presence of this lesion, so often silent in the earlier stages, should be looked for in all patients over 50. Positive occult blood in the stools and the presence of a polymorph leucocytosis are suggestive signs.

Hiatus hernia is quite common in women over 55; the persistent blood loss is said to be due to the trauma suffered by the part of the stomach herniated into the chest. Barium meal examination shows its presence.

Ulcerative colitis is a cause of iron-deficiency anæmia in the younger adults; usually the history of recurrent diarrhœa with blood in the stools directs attention to the colon. Sigmoidoscopy and barium enema will confirm the diagnosis.

Crohn's disease is sometimes discovered in the course of this investigation.

Œsophageal varices are often only found after the patient has had a hæmatemesis and enlargement of the liver and spleen have been found. There are milder cases, especially in young adults, in which small recurrent leakage occurs and eventually causes a typical iron-deficiency anæmia. X-ray examination of the œsophagus by the barium swallow technique will usually show the varices.

Sources of Blood Loss. B. Menorrhagia: Chronic excessive loss at menstruation is a common cause of iron-deficiency anæmia. Sometimes the loss has been increasing over a period of a year or more, or menstruation may occur more frequently than normal, or be prolonged beyond the usual time. It is, of course, essential to find out if any local disease of the genital tract is responsible for the menorrhagia, but experience has shown that in many patients treatment of the anæmia is followed by relief of the menorrhagia. If any clear physical signs of genital tract involvement are present, the patient should be sent for a gynæcological consultation without delay; in other cases it is reasonable to wait until the anæmia is relieved and send the patient for further consultation only if the menorrhagia persists.

Sources of Blood Loss. C. Hæmorrhagic diseases: The chronic and recurrent blood loss that is a feature of these diseases often leads to iron-deficiency anæmia. Thrombocytopenic purpura and hæmophilia are examples of this group of diseases that can cause iron-deficiency anæmia. The diagnosis of hæmorrhagic disease is not usually difficult since it is the hæmorrhages and not the anæmia that is the patient's main complaint. Menorrhagia causing anæmia is occasionally the presenting symptom of thrombocytopenic purpura; the platelet count which should be part of the investigation of such a case will be low and direct attention to the correct diagnosis.

2. Conditions Causing Malabsorption of Iron

Some degree of poor absorption of iron from food probably occurs in every patient with iron deficiency anæmia. Much experimental work has shown that the proportion of iron in the food that can be absorbed is *increased* in patients whose body stores of iron are low; normally 5–10 per cent is absorbed, but in iron deficiency the figure can rise to levels like 45 per cent. Nevertheless, there seems to be a limit to the absolute amount of iron that can be transferred across the alimentary mucosa; according to Finch, this is about 5 mg. daily. This is a very small amount compared with the therapeutic doses of iron that have been found necessary, which are of the order of 200 mg. of iron daily.