# Tutorials in Surgery 5

## Surgical Pathology II

F G Smiddy
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# Preface

Accurate diagnosis is the most important and challenging facet of medical practice since without it treatment is ineffective. This book is intended to help both prospective and established surgeons to understand the basic pathology of the diseases which present for surgical treatment. A surgeon is a physician who treats a pathological condition, where thought necessary, by operation. A pathologist is a physician who, because of his knowledge of disease processes, plays an essential role in accurate diagnosis. Both should be concerned with the sick individual as a whole who is liable to suffer the protean problems which can arise in any pathological situation. It is, therefore, imperative that the pathologist is given full access to all the relevant clinical information about a particular patient. The pathologist employs a microscope and not a crystal ball. Rapport between the surgeon and pathologist must be complete, not only for the help they can give each other but for the benefit of the patient.

Because this text is aimed at the practising surgeon rather than the 'pure' pathologist, an attempt has been made to describe the clinical effects of each pathological condition before passing on to a consideration of the gross and microscopic pathology.

We have tried, albeit perhaps imperfectly, to produce a text after the fashion of the father of the Leeds School of Surgery, Lord Moynihan, who coined the phrase 'the pathology of the living'.

F G Smiddy
P N Cowen

# Acknowledgements

*Tutorials 4 and 5* on the subject of Surgical Pathology could obviously not have been written without the assistance of many others in addition to the authors themselves.

It therefore gives us great pleasure to acknowledge the assistance we have received from Mr S Toms and Mr P Hargreaves who were responsible for producing the illustrations. We are also indebted to Dr C R Abbott and Dr C K Anderson for advice and access to their pathological material and, in general terms, to the Pathological Department for access to specimens.

A handwritten folio must be converted into typescript and, as always, Mrs P M Docherty gave her whole-hearted attention to this matter. Finally the typescript must be edited in such a way that it becomes a textbook, and knowing the expertise required for this task the authors gratefully acknowledge the work of Mrs Susan Brown.

F G Smiddy
P N Cowen
Leeds 1984

# Contents

# 1 Blood disorders of special interest to the surgeon



## 1.1 Genetically determined defects of the red cell

**Hereditary spherocytosis** (Figs. 1.1, 1.2)

This condition, caused by a membrane defect of the red cell, is inherited as an autosomal dominant trait with incomplete penetrance. However, in 25 per cent of cases there is no family history.

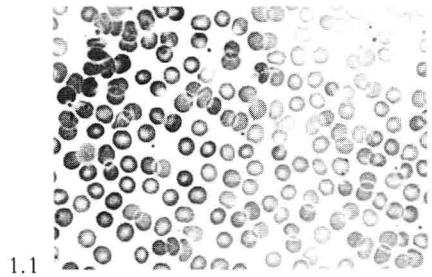
The membranes of the erythrocytes become permeable to sodium ions and in addition, because some lipid is lost from them, the erythrocytes are smaller than normal and tend to assume a spherical shape instead of the normal biconcave configuration.

These microspherocytes are trapped in the splenic red pulp because they lack the necessary pliability to pass between the endothelial cells to return to the circulation. Subsequently they are lysed causing the attacks of haemolytic acholuric jaundice which are a particular clinical feature of this condition.

*Clinical presentation*

As stated, the characteristic feature of this disease is intermittent jaundice which usually dates from childhood. The attacks of jaundice are not necessarily associated with anaemia but this may occur following an infection or, in the adult female, pregnancy. In these circumstances rapidly increasing jaundice, fever and leucocytosis occur. Such a 'crisis' may be due either to an increase in red cell destruction in which case there is an associated reticulocytosis or to a decrease in erythrocyte production in the marrow.

Moderate splenomegaly is found in all patients and, in some, chronic ulceration of the legs occurs.



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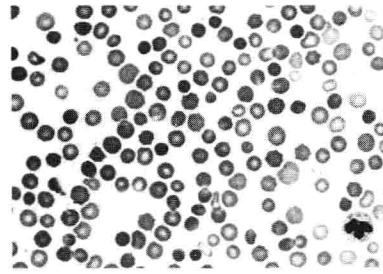

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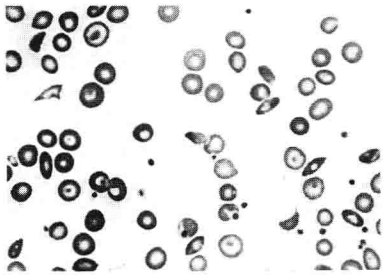

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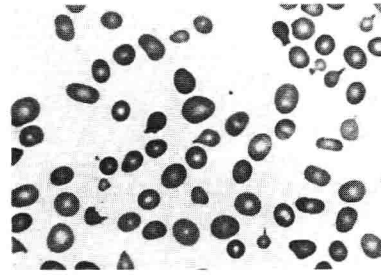

1.4

***Fig. 1.1 Normal blood film*** *(all films (Figs 1.1–1.4)) stained May-Grunwald Giemsa)*

***Fig 1.2 Hereditary spherocytosis*** *Many of the erythrocytes are smaller than normal and stain darker because, being spherical or biconvex instead of biconcanve discs, the normal central pallor is missing.*

***Fig 1.3 Sickle cell anaemia*** *Characteristic sickle-shaped erythrocytes are present. Other erythrocytes tend to be smaller and paler than normal indicating iron deficiency (the anaemia is partly haemolytic).*

***Fig 1.4 Macrocytic blood film*** *(megaloblastic or macrocytic anaemia) The erythrocytes vary in size (anisocytosis), tend to be large (macrocytosis), have a full complement of haemoglobin which causes dark staining (hyperchromasia) and occasionally have irregular shapes (poikilocytosis).*

The diagnosis is confirmed by demonstrating the increased fragility of the red cells when placed in hypotonic saline solution. Normal red cells lyse at concentrations of sodium chloride between 0.42% and 0.46% or even lower. Lysis beginning in an 0.5% solution is abnormal and indicates increased fragility.

The surgeon's interest in this condition lies in the fact that although the membrane defect cannot be rectified a clinical cure can be achieved by splenectomy.

**Sickle cell anaemia** (Fig. 1.3)

This condition, which is also hereditary, is due to the presence of abnormal haemoglobin within the red cell. It belongs, therefore, to the group of diseases known as the haemoglobinopathies.

Normal haemoglobin is a globular protein with a molecular weight of 68 000. The molecule is composed of a protein, globin, attached to non-protein prosthetic haem groups. The haemoglobinopathies are due to the synthesis of an abnormal globin fraction and many have been described. The abnormal haemoglobin in sickle cell anaemia is haemoglobin-S.

Sickle cell disease occurs in negroes homozygous for the abnormal gene. In the heterozygous individual there is minimal or no overt evidence of the disease but a 'sickling trait' is present which can be demonstrated by exposing the erythrocytes to a reducing solution.

As a result of valine replacing glutamic acid in the amino-acid sequence, the affected haemoglobin molecules, when reduced, develop an abnormal configuration which causes the red cells to become distorted. Such appearances become prominent when a reducing agent is added to a sample of blood taken from an affected individual. To confirm the diagnosis, electrophoresis can be used to demonstrate the abnormal haemoglobin-S.

Clinically, hypoxic episodes induce sickling crises and in addition leg ulceration, recurrent respiratory infection and cardiomyopathy occur. The disease may be fatal in childhood. These effects are caused by the blocking of the smaller blood vessels by sickled cells, with the result that infarction of tissue occurs.

Surgical interest in this disease lies in the knowledge that a general anaesthetic may precipitate a crisis if a period of hypoxia occurs. In all negro patients or patients of negroid stock, therefore, screening tests should be applied. Furthermore, a postoperative chest infection or massive pulmonary collapse may precipitate sickling, possibly because of changes in the $pO_2$. In this disease a tourniquet should not be applied to a major limb since sickling may occur in the blood distal to the tourniquet, with resultant infarction after it is released.

## 1.2 Autoimmune haemolytic anaemia

This condition is due to the development of autoantibodies of the cytotoxic type which can bind to and damage an individual's own red cells.

The antibodies formed may belong to one of two classes. Those of the IgG class generally react at 37°C and are, therefore, known as 'warm' antibodies. A red cell coated with such an antibody commonly becomes microspherocytic and undergoes lysis in the spleen. The clinical picture, therefore, resembles hereditary spherocytosis except that the condition rarely occurs in childhood and is most commonly seen in women over 40 years of age. Approximately

half of the cases arise spontaneously and in the remainder a wide spectrum of diseases, including systemic lupus erythematosus, rheumatoid arthritis and malignant lymphoma precipitate the condition.

Whilst the majority of affected individuals can be successfully treated by corticosteroids occasionally the surgeon may be asked to perform a splenectomy if medical treatment fails. The sequestration of $^{51}$chromium tagged erythrocytes in the spleen has been proposed as an indication for splenectomy but it is a test of doubtful predictive value.

The second class of antibodies which gives rise to this type of anaemia is IgM. This characteristically reacts at temperatures below 37°C and is, therefore, known as a cold antibody. This type of antibody may give rise to Raynaud's phenomenon on exposure of the limbs to cold. The surgeon cannot influence the course of this condition but note should be taken of the possibility of its existence when confronted by a patient presenting with a vasospastic disorder of the limbs.

## 1.3 Megaloblastic anaemia

In this type of anaemia a megaloblastic change is seen in the bone marrow due to arrest of cell maturation resulting from vitamin $B_{12}$ or folic acid deficiency. In addition to the red cells, both the granulocytes and platelets are also affected but by far the most conspicuous feature of this condition is the alteration in erythropoiesis.

Whilst a megaloblastic anaemia may be found during the routine investigation of a surgical patient, the surgeon himself may be responsible for causing it. The common causes of iatrogenic vitamin $B_{12}$ and folic acid deficiency include:

1 *Total gastrectomy.* $B_{12}$ deficiency inevitably follows this operation because the source of intrinsic factor which is required for its absorption is removed. However, since advanced carcinoma of the stomach is the usual reason for total gastrectomy it is unusual for the patient to survive long enough to develop anaemia because the liver stores of vitamin $B_{12}$ are normally adequate for several years.

2 *Partial gastrectomy.* A small proportion of patients in whom a partial gastrectomy has been performed ultimately develop a megaloblastic anaemia due to a lack of the intrinsic factor. This is due to the development of an atrophic gastritis which, in turn, is the result of bile regurgitation into the stomach.

3 *Blind loop syndrome.* Blind loops produced by by-pass operations on the small bowel or by side-to-side anastomoses instead of end-to-end anastomoses may cause a megaloblastic anaemia by creating an environment in which the normal ecology of the small gut is greatly altered. In these situations the abnormal bacterial flora which proliferates within the blind loop takes up the

intrinsic factor-$B_{12}$ complex so that it is no longer available for absorption and, as a result, a megaloblastic anaemia eventually develops.

A similar situation may develop in naturally occurring jejunal diverticulae.

4 *Malabsorption.* Interference with the absorption of the intrinsic factor-$B_{12}$ complex occurs when extensive disease of the ileum is present, as in Crohn's disease, or when extensive resections of the small bowel have been performed.

The chief effects of a megaloblastic anaemia are as follows:

1 In the peripheral blood a pancytopenia develops. The red cells show megaloblastic features such as an increase in MCV and, as the disease progresses, anisocytosis and poikilocytosis (Fig. 1.4) occur together with the appearance of nucleated red cells.

2 In the bones there is marked expansion of the red marrow which replaces the pale fatty marrow of the long bones ultimately occupying the entire length.

Cytologically all the cellular elements associated with haemopoiesis are affected; the essential feature being the arrest of maturation of the developing red cells.

3 In the nervous system the principle lesion is subacute combined degeneration of the cord together with a peripheral neuropathy. These changes may develop even when the anaemia itself is mild and subclinical.

## 1.4 Transfusion reactions

Many iso-antibodies have been discovered in relation to the erythrocytes but the most important still remain those of the ABO and Rhesus systems. Others such as the anti-E and anti-Kell can be detected by screening but do not have the same clinical importance.

The ABO specificity of red cells is determined by glycoproteins and glycolipids both carrying the same immunodominant sugar. The same antigens are present in human mucous secretions, e.g. ovarian cyst fluid, gastric juice and saliva, in individuals who are secretors, i.e. who possess the iso-antigen A, B and AB. Although Group O has neither antigen in the cell membrane the antibody in the serum is both anti-A and anti-B.

When incompatible blood is transfused into a recipient in whose circulation the appropriate antibodies are already present, a haemolytic reaction occurs and the transfused cells are rapidly destroyed. The results of an incompatible blood transfusion depend upon the speed of haemolysis and the volume of incompatible blood which has been administered.

An incompatible transfusion is followed by a sensation of heat and pain along the course of the vein into which the mismatched blood is being transfused, accompanied by facial flushing, rigors and loin pain together with a

feeling of constriction in the chest. A severe reaction will result in hypotension and shock and if recovery occurs haemoglobinuria will follow together with the appearance of methaemalbumin in the urine.

The major pathological changes are seen in the kidneys which become oedematous and infiltrated with leucocytes. A severe reaction results in acute tubular necrosis leading to renal failure.

The precise volume of incompatible blood required to cause death is unknown but in one reported series no deaths occurred when less than 350 ml had been administered.

The commonest causes of an incompatible blood transfusion are misidentification of the patient and technical failure to detect incompatibility. Unfortunately and unforgivably the former is commoner than the latter.

So far as the Rhesus (Rh) system is concerned a reaction occurs if Rh positive blood is administered to a Rh negative patient who has been previously immunized by a transfusion of Rh positive blood or by a pregnancy in which the fetus carried Rh antigens, i.e. had Rh positive blood. In this situation the mother is sensitized in the first pregnancy during parturition due to fetal blood gaining access to the maternal circulation through the placenta.

## 1.5 Haemostatic defects

### Haemophilia

This condition is normally inherited as a sex-linked recessive characteristic, the male exhibiting the disease and the female acting as a carrier and transmitting it to the next generation. The disease can occur in the female when an affected male mates with a female carrier but this is rare. In about one-third of all cases there is no family history suggesting that a spontaneous mutation has occurred.

*Clinical presentation*

The clinical presentation of haemophilia depends upon the severity of the condition, which is measured by the degree of deficiency of the procoagulant activity of Factor VIII. In severe cases it will be noted in early childhood that comparatively minor trauma leads either to excessive bruising, the development of a haemarthrosis or persistent bleeding if the skin or a mucous membrane is torn or cut. Severe bleeding into the soft tissues is eventually followed by fibrosis and diminished function and severe bleeding into joints leads eventually to destruction of the articular cartilage which causes crippling.

*Pathology*

The underlying pathological feature of haemophilia is a deficiency of the

procoagulant activity of Factor VIII which may be as low as 1 to 2 per cent of normal.

The disease is usually suspected from the clinical history and confirmed when a normal platelet count is found along with a normal bleeding and prothrombin time. Further investigation shows that the Kaolin Cephalin time is prolonged and accompanied by lower than normal levels of prothrombin, Factor VIII and Factor IX.

A similar deficiency in Factor IX causes the much rarer Christmas disease, sometimes referred to as haemophilia B to distinguish it from classical haemophilia, haemophilia A. The latter is 10 times commoner than the former, although still a rare condition; only about 3,000 cases of haemophilia A existing in the UK.

The importance of this disease to the surgeon lies in the need to restore the Factor VIII to near normal levels if the condition is already recognized and a surgical procedure is indicated. This is normally performed by the use of cryoprecipitate or AHF concentrate.

### Von Willebrand's disease

This condition is due to a deficiency of 'Factor VIII-related antigen'. Once this factor has been infused into a patient suffering from this deficiency he or she can then produce Factor VIII procoagulant activity. This response can be obtained even when haemophiliac plasma is used since the haemophiliac still possesses the Factor VIII-related antigen.

### **Disseminated intravascular coagulation** (defibrination syndrome)

This condition is due to the widespread activation of the coagulation factors of the blood. Clinically, acute purpura develops or severe bleeding takes place from the gastrointestinal, urinary or genital tracts. Alternatively, chronic thrombotic manifestations may predominate.

This condition is always secondary to some underlying pathological process and those of most importance to the surgeon include:

(a) bacteraemic shock;
(b) burns;
(c) disseminated malignancy, particularly of the prostate and pancreas;
(d) cardiac arrest and resuscitation.

*Pathogenesis*

When the normal haemostatic system of the body is rallied, thrombin or thrombin-like substances are released into the circulation. These include the products of tissue trauma. Amniotic fluid emboli, snake venom, endotoxins and antibody-antigen complexes act similarly. All cause a complex series of