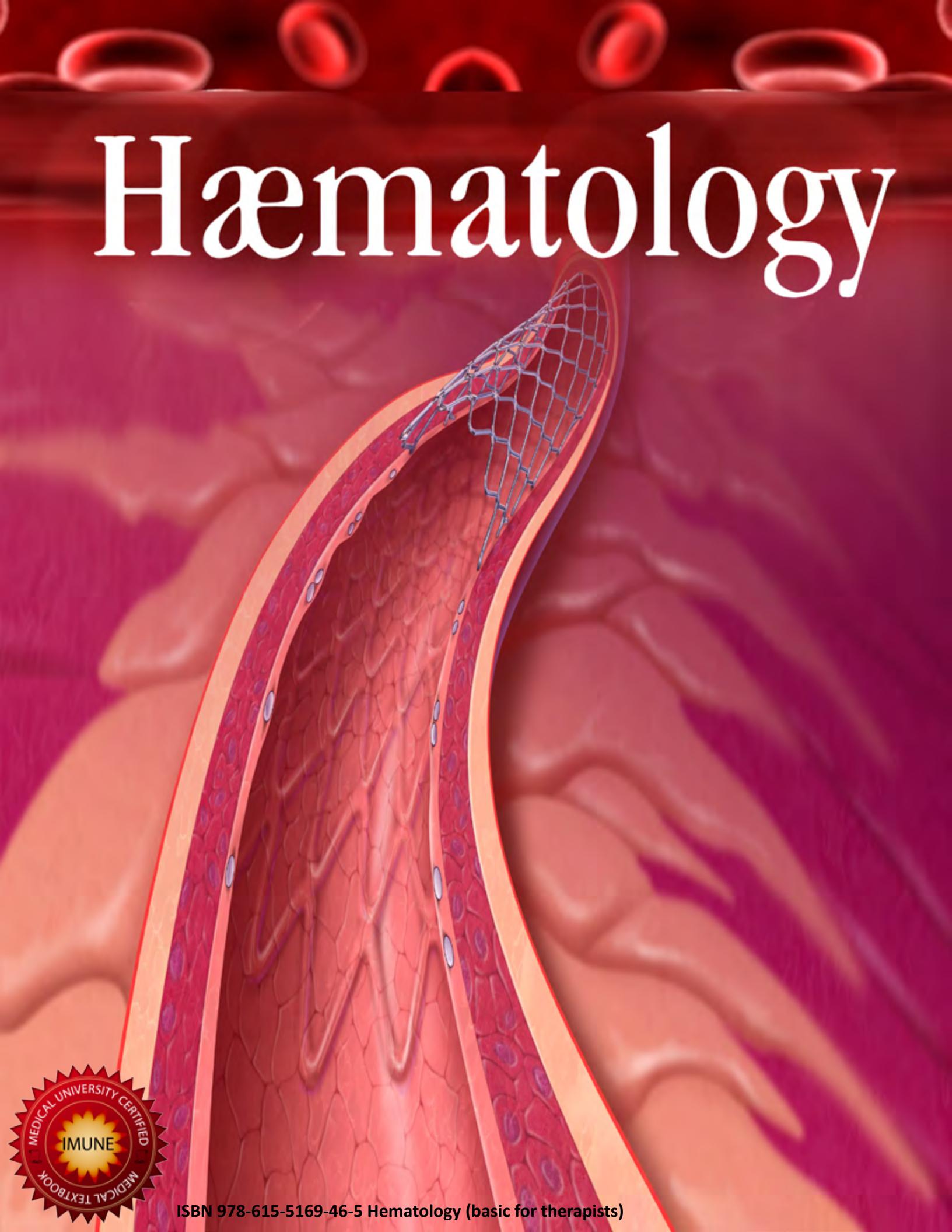


# Hæmatology



ISBN 978-615-5169-46-5 Hematology (basic for therapists)

## Hematology

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### HISTORY TAKING

Abnormalities of the blood are associated with a wide range of symptoms and these are discussed in detail under diagnostic headings in subsequent parts of the book. The intention of this section is to give an overview of history taking in patients with blood disorders. Despite the advent of sophisticated laboratory equipment to test blood, a thorough history remains fundamental to accurate diagnosis. In practice the history may precede and then follow the knowledge of a laboratory test abnormality. Whatever the order of events, only by considering symptoms, physical signs and laboratory results in conjunction can the correct conclusion be reached and the patient managed in the appropriate psychosocial setting.

### HISTORY OF THE PRESENTING COMPLAINT

A few patients are asymptomatic and have an unpredictable abnormality detected on a routine blood count. Most patients present to the doctor with complaints dependent on the nature of the change in the blood. Some will have several blood abnormalities and present with a large number of symptoms. Despite this complexity it is possible to highlight some common groups of symptoms (Table 1).

#### **Symptoms attributable to anaemia (low haemoglobin concentration)**

Patients with anaemia have a reduced supply of oxygen to the tissues. Symptoms include fatigue, weakness, dyspnoea, palpitations, headaches, tinnitus and chest pain (due to exacerbation of angina). The symptoms are affected not only by the severity of the anaemia but by its speed of onset. Anaemia which develops rapidly is usually less well tolerated and patients are more debilitated.

**Symptoms attributable to a low white cell count (leucopenia)** It is usually a reduction in neutrophils (neutropenia) which causes clinical problems. Patients are susceptible to infections, the risk rising sharply at neutrophil counts below  $0.5 \times 10^9/l$ . Serious blood diseases such as acute leukaemia can present as life-threatening infections or as apparently trivial infections (e.g. a sore throat) which are unusually refractory to treatment. Perineal sepsis can be a particular problem.

#### **Symptoms attributable to a low platelet count (thrombocytopenia)**

Thrombocytopenia leads to a haemorrhagic tendency and common presentations include epistaxes (nose bleeds), bleeding from gums, menorrhagia (heavy periods) and excessive bleeding after trauma or surgery. Patients may also complain of easy bruising or a petechial rash. Spontaneous bleeding is usually restricted to platelet counts below  $20 \times 10^9/l$ . In disorders of platelet function similar symptoms may occur even when the count is normal.

#### **Symptoms attributable to abnormal coagulation**

Patients with a defect in the coagulation cascade (e.g. low factor VIII level in haemophilia A) bleed easily after surgery and trauma but the pattern of spontaneous haemorrhage is normally

different to that seen in platelet disorders. The commonest complaints are of bleeding into joints (haemarthroses) and muscles. Lifelong symptoms suggest an inherited abnormality whilst recent onset is consistent with an acquired aetiology.

#### Symptoms attributable to infiltration by malignancy

Malignant disorders of the blood such as leukaemias and lymphomas have the capacity to invade tissues. Patients may complain of lumps in the neck, axillae or groin caused by lymphadenopathy or of abdominal pain or distension caused by splenomegaly. Involvement of the nervous system may manifest as headache, pain in dermatomal distribution or loss of function.

The severity, quality and temporal characteristics of pain may or may not be helpful in identifying an underlying blood disorder. The pain of the vaso-occlusive crisis of sickle cell anaemia is often distinctive whereas the chronic low back pain of myeloma is all too easily dismissed.

A thorough systemic enquiry is essential as blood abnormalities are more often caused by a systemic disease than by a specific blood disease. It can be difficult to establish whether the primary problem is in the bone marrow or if the blood is 'reacting' to pathology elsewhere. One example is a high platelet count (thrombocytosis). This may be caused by the bone marrow disorder *essential thrombocythaemia* but equally can be secondary to infection, inflammation or malignancy ('reactive thrombocytosis'). Only by excluding a non-haematological aetiology can the diagnosis of *essential thrombocythaemia* be confidently made. On occasion the haematological diagnosis prompts a return to a particular part of the systemic enquiry. Thus the finding of unexplained iron deficiency necessitates an exhaustive enquiry for symptoms of gastrointestinal disease associated with chronic blood loss.

#### PAST MEDICAL HISTORY

It is important to elicit a history of diseases which may have caused a haematological abnormality or which may affect the management of a primary blood disorder such as leukaemia. Where there is a known abnormality in the blood count it is helpful to establish whether previous counts have been performed. Where past results are available they will clarify whether the problem is of recent onset or longstanding. For patients presenting with easy bruising or bleeding, previous surgical exposure is of particular interest. The lack of excessive bleeding after surgery suggests that either the bleeding tendency is of limited significance or of more recent onset.

#### DRUG HISTORY

Drugs can cause haematological problems - some commoner examples are listed in Table 2. A careful drug history (wherever possible verified by checking tablets) may suggest a likely offending agent. If the problem is of sufficient severity to cause concern the drug should ideally be discontinued and the blood count monitored to check resolution. It is as relevant to obtain a history of allergy in haematology as in other areas of medicine. Indeed, patients with haematological malignancies are often given an unusually large number of chemotherapeutic and antimicrobial agents and possible reactions have to be vigilantly documented to avoid

repeat exposure.

#### FAMILY HISTORY

As can be seen from Table 3, a number of blood diseases are inherited. A knowledge of the mode of inheritance is useful in diagnosis and essential in counselling the patient and family. A simple question as to the presence of 'anaemia' or a 'bleeding problem' in other family members can prevent unnecessary investigation and delay in diagnosis.

#### SOCIAL HISTORY

With the growing reliance on technology for diagnosis and treatment it can be surprisingly easy to forget that a blood disorder is affecting a 'real person'. An understanding of the patient's normal lifestyle is particularly important where a chronic or serious disease is diagnosed. Many people developing haematological malignancies are elderly and need support in the community including, perhaps, visits by social workers and nurses. Often such diseases are incurable and expert management of symptoms has to be complemented by an understanding of the patient's need to sort out affairs and communicate the news to family and friends. In working adults the onset of diseases like leukaemia with frequent clinic visits and hospitalisation can lead to unemployment and marital and financial difficulties. In children chronic blood disorders such as haemophilia and the haemoglobinopathies may cause time lost from school and create stresses for the whole family. Good practice of clinical haematology requires consideration of the far-reaching effects of the diagnosis and necessary treatment on the patient.

#### MISCELLANEOUS

*Alcohol* misuse can cause blood changes, the most common being macrocytosis (enlarged red cells). A positive history will prevent unnecessary investigation for other causes. *Smoking* is a cause of moderate polycythaemia (elevated haemoglobin) and appears to be associated with an increased incidence of acute leukaemia. *Travel* to tropical areas raises the possibility of malaria and other tropical diseases which can affect the blood.

#### History taking

- In the diagnosis of blood disorders, the history is core to the clinical examination and laboratory testing.
- Blood abnormalities such as anaemia, leucopenia and thrombocytopenia lead to predictable groups of symptoms.
- Blood abnormalities may be caused by systemic diseases, familial disorders and drugs. A thorough systemic enquiry, past medical history, drug history and family history should be elicited.
- Serious and chronic blood diseases (e.g. leukaemia, haemoglobinopathies, and

haemophilia) have major social implications for children and adults; these should be explored not ignored.

**Table 1 Common haematological abnormalities and associated symptoms**

Anaemia	Fatigue, weakness, dyspnoea, palpitations, headache, dizziness, tinnitus
Leucopenia (particularly neutropenia)	Unusually severe or recurrent infections
Thrombocytopenia	Easy bruising, excessive bleeding after trauma, spontaneous bleeding from mucous membranes
Defective coagulation (e. g. key factor deficiency)	Excessive bleeding after trauma, spontaneous bleeds into joints and muscles
Infiltration by malignancy (e. g. leukaemia, lymphoma)	'Lumps' caused by lymphadenopathy, pain, neurological symptoms

\* The haematological abnormalities have many possible causes but will always tend to lead to the symptoms shown.

**Table 2 Possible haematological side-effects of drugs**

Marrow aplasia	Chloramphenicol (idiosyncratic) Cytotoxics (dose-related)
Haemolytic anaemia	Methyldopa Penicillins
Leucopenia/agranulocytosis	Phenothiazines Sulphonamides
Thrombocytopenia	Quinine Thiazide diuretics

\*Many drugs have been implicated in all these abnormalities - the examples shown are some of the more common offenders.

**Table 3 Some inherited blood disorders**

<b>Red cell disorders</b>	<b>Disorders of the membrane</b>	<b>Hereditary spherocytosis and elliptocytosis</b>
Disorders of haemoglobin		Thalassaemias and sickle syndromes
Disorders of metabolism		Glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies
Factor deficiency		Haemophilia A and B
Combined factor and platelet abnormality		Von Willebrand's disease
Platelet abnormality		Bernard-Soulier syndrome (rare)
<b>White cell disorders</b>		Rare functional disorders (e.g. chronic granulomatous disease)

The mode of inheritance of these disorders is discussed in the relevant sections.

Abnormalities of the blood may arise as a result of a primary disorder of the bone marrow (e.g. leukaemia) or from a wide range of systemic disorders. A thorough clinical examination is vital both to confirm a likely diagnosis and to exclude coexistent problems. There is not space here to detail all the elements of clinical examination; we have concentrated on aspects of the examination most relevant to patients with a primary blood disorder.

## LOOK AT THE PATIENT!

It is easy to examine a patient carefully without properly observing them. A deliberate inspection of the patient's face whilst taking the history may reveal vital clues even before the formal examination is commenced. Common examples include the pallor of iron deficiency anaemia, the lemon tint of megaloblastic anaemia, the jaundice of a haemolytic anaemia, and the plethora of polycythaemia. Before laying a hand on the patient, a careful inspection of the mouth and skin may also point to particular blood abnormalities or disorders (Table 1). The patient's ethnic origin can be of relevance. Sickle cell anaemia is an unlikely diagnosis in a patient with white skin while pernicious anaemia is equally unlikely in a patient with black skin. Children with chronic blood disorders such as haemoglobinopathies are frequently thinner and shorter than their healthy peers.

## GENERAL EXAMINATION

Careful observation should be followed by a methodical examination of the major systems. The possible abnormalities in each system which may be seen in blood diseases are too numerous to detail here. They are referred to in the relevant sections describing each disease. Although examination should be ordered, in a busy clinical practice it is often necessary to prioritise.

Rectal examination is not routine in all patients with blood disorders but is definitely indicated in unexplained iron deficiency to exclude an otherwise asymptomatic rectal carcinoma; it is contra-indicated in patients with suspected leukaemia and neutropenia. Similarly, an exhaustive examination of the major joints is not universally performed but is crucial in a patient with haemophilia.

**Table 1 Observation of the patient with a blood disorder.**

Some common signs and their possible clinical relevance.

Clinical sign	Possible haematological abnormality
<b>Face</b>	
Pallor	Any anaemia
Lemon tint	Megaloblastic anaemia
Jaundice	Haemolytic anaemia
Plethora	Polycythaemia
<b>Mouth</b>	
Ulcers	Neutropenia
Glossitis	Megaloblastic anaemia
Angular stomatitis	Iron deficiency anaemia
Candida ('Thrush')	Iron deficiency anaemia Immunosuppression
<b>Skin</b>	
Pallor	Any anaemia
Jaundice	Haemolytic anaemia
Excessive bruising	Coagulation disorder, thrombocytopenia
Purpuric / Pelechial rash	Thrombocytopenia
Leg ulcers	Sickle cell anaemia

## EXAMINATION OF THE LYMPH NODES

Lymph nodes may be enlarged in primary blood disorders and systemic diseases. Enlargement is referred to as 'lymphadenopathy' or just 'adenopathy'.

The differential diagnosis differs in generalized and localised forms of lymphadenopathy (Table 2). In practice, palpable lymphadenopathy is usually limited to the cervical, axillary and inguinal areas.

Enlargement of the *cervical lymph nodes* is the most common cause of a swelling in the neck and, if massive, may be easily visible. Following careful inspection of the neck, it is easiest to examine the cervical nodes from behind the seated patient, methodically palpating the anatomical areas detailed. As for all lumps it is important to document not only the size and location of enlarged nodes, but also the shape, consistency and presence of tenderness. Lymphadenopathy secondary to infection is more often tender than that due to malignancy.

Nodes involved by carcinoma are characteristically stony hard whilst those involved by lymphoma are more 'rubbery'. The presence of cervical adenopathy should always prompt a thorough examination of the head and neck to detect a local cause (e.g. malignancy or infection); formal ear, nose and throat examination is often indicated.

The *axillary nodes* are best examined with the patient supine and the arm supported by the side,

the examiner using the right hand to gently palpate the left axilla and the left hand for the right axilla. Anatomically, the nodes are divided into medial, lateral, posterior, central and apical groups. Examination of *inguinal nodes* is most easily performed whilst examining the abdomen. Care must be taken not to confuse inguinal adenopathy with an irreducible femoral hernia. Enlarged abdominal lymph nodes may cause an abnormal fullness of the central abdomen on palpation.

On occasion it is difficult to be certain that nodes are pathologically enlarged. Interpretation must take account of the patient's age and occupation. Large tonsillar glands are common in children, whilst people exposed to repeated minor injuries of the hands and feet often have some lymphadenopathy in the draining areas. A period of observation can be helpful. If serious doubt persists then a surgical biopsy is indicated.

**Table 2 Common causes of lymphadenopathy**

### Localised

Local bacterial or viral infection  
Lymphoma  
Metastatic malignancy

### Generalised

Systemic Infection  
- bacterial (e.g. tuberculosis)  
- viral (e.g. Epstein-Barr, HIV)  
Lymphoma  
Other haematological malignancy (e.g. leukaemia)  
Inflammatory disease (e.g. connective tissue disorder, sarcoid)  
Disseminated malignancy

## EXAMINATION OF THE SPLEEN

The spleen is enlarged in many blood disorders and in some systemic diseases (Table 3). The presence of a palpable spleen and its characteristics often narrow the differential diagnosis considerably. Examination of the spleen is frequently done badly. It is easy to miss a slightly enlarged spleen which is just palpable ('tippable') and it is also embarrassingly easy to miss a spleen which is massively enlarged. However, neither of these mistakes are likely if the examination is conducted as below.

The patient should be examined on a suitable examination couch or bed and should be encouraged to relax. The whole abdomen is exposed - ideally from the nipples to the knees. The examiner sits or kneels to allow palpation with a (warm) hand with the forearm horizontal to the abdomen. First, the abdomen is inspected for a visible mass and the patient is asked if they have any abdominal tenderness.

It is normal to palpate the whole abdomen and then examine the major organs in turn. The spleen enlarges from below the tenth rib along a line heading for the umbilicus. Palpation for the spleen is commenced in the right lower quadrant of the abdomen, otherwise massive enlargement can be missed. The hand is moved in stages towards the tip of the left tenth rib whilst the patient takes deep breaths. The edge of an enlarged spleen connects with the tips of

the index and middle fingers during deep inspiration. If the spleen is not palpable using this technique, it is worth rolling the patient slightly onto the right side with the examiner's left hand held firmly behind the left lower ribs. This latter manoeuvre may lift forward a slightly enlarged spleen and make it palpable on deep inspiration.

The following features are typical of an enlarged spleen:

- It has a characteristic shape and sometimes a palpable notch on its upper edge
- You cannot get above it
- It moves with respiration
- It is dull to percussion
- It cannot be felt bimanually or balloteted.

In practice an enlarged spleen is most likely to be misidentified as an enlarged left kidney. However, the kidney is not dull to percussion (it is covered by the colon) and it can be felt bimanually and balloteted. It is worth listening with a stethoscope over an enlarged spleen as inflammation of the capsule may cause an audible 'splenic rub'. The spleen is usually uniformly enlarged and it is not generally possible to identify the underlying disorder by palpation alone. The degree of enlargement does, however, give a diagnostic clue (Table 3).

### Examining the patient

- The clinical examination is an important part of the diagnosis of blood disorders. It is helpful to carefully observe the patient prior to the formal examination of systems.
- In routine clinical practice some aspects of examination are prioritised (e.g. rectal examination in unexplained iron deficiency).
- Proper examination of the lymph nodes requires familiarity with the normal anatomical groups and the causes of enlargement.
- Examination of the spleen is frequently badly performed; with poor technique even massive

**Table 3 Common causes of splenomegaly**

Degree of enlargement	Centimetres palpable Below costal margin	Causes
Slight	0 – 4	Various acute and chronic infections (e.g. septicaemia, tuberculosis)
Moderate	4 – 8	Haemolytic anaemia Infectious mononucleosis Portal hypertension
Massive	Greater than 8	Myelofibrosis Chronic myeloid leukaemia Primary polycythaemia Lymphoma

Malaria  
Leishmaniasis

**Note:** The division by size is clinically helpful but disorders associated with massive splenomegaly may also cause lesser degrees of enlargement.

Diagnosis of most blood disorders is possible from a combination of clinical history, clinical examination and relatively routine laboratory tests. Haematology laboratories are now heavily dependent on complex electronic machinery. The ubiquitous full blood count (FBC) is the archetypal haematological investigation and is performed by specialised automated cell counters. However, despite the accessibility of modern technology, the more simple traditional techniques of blood and bone marrow film spreading, staining, and light microscopy remain essential parts of the haematologist's repertoire.

### THE BLOOD COUNT

Many of the diseases discussed in this book are first suggested by an abnormality in the blood count (often referred to as the full blood count). The test is performed on a small specimen of anticoagulated venous blood; the normal anticoagulant is ethylene diamine tetra-acetic acid (EDTA). As can be seen it contains a large amount of numerical information pertaining to the three cell lines in the peripheral blood: red cells (and haemoglobin), white cells (with a differential count of each specific cell type) and platelets.

When interpreting the report it is sensible to initially focus on the haemoglobin (Hb) concentration, total white cell count (WCC) and platelet count - most blood abnormalities of clinical significance are associated with a derangement of at least one of these values. Much of the remaining information details the nature of the red cells and their degree of haemoglobinisation, and the precise make-up of the white cell count. The former values are helpful in the diagnosis of anaemia, and the latter in the diagnosis of a variety of diseases of white cells (e.g. leukaemias) and reactions to systemic disease. To understand the role of the automated blood count in clinical practice, and particularly its limitations, it is helpful to understand how the numerical values are generated.

### Automated haematology counters

The two essential functions of the automated blood cell counter are the measurement of Hb concentration in the blood and the counting and sizing of blood cells.

Most counters use a modification of the traditional cyan-methaemoglobin method to measure Hb concentration. In essence, blood is diluted in a solution where Hb is converted to cyanmethaemoglobin and then the Hb concentration derived from the light absorbence (optical density) of the resultant solution measured by a spectrophotometer. Automated machines have at least two channels for cell counting. In one, red cells and platelets may be counted and in the other red cells are lysed leaving white cells for analysis. Extra channels are often used for differential white cell counting and reticulocyte counting. There are two basic methods for cell counting and sizing: electrical impedance and light scattering.

The electrical impedance method relies on blood cells being very poor conductors of electricity.

Thus, when the cells are passed in a stream through a narrow aperture across which an electrical current is maintained the individual cells create an increase in electrical impedance of a size proportional to the cell volume. In the light scattering method the cells deflect a beam of light (often a laser beam) and a detector converts the scatter into pulses proportional to cell size. For sophisticated measurements such as the differential white cell count the two methods can be used together with addition of other modalities reliant on biochemical reactions and light absorbence.

Sophisticated though this technology is, automated cell counters are ultimately no substitute for the trained human eye. Results outside the machine's numerical normal range or the presence of unusual circulating cells (e.g. leukaemic cells) should be flagged as being abnormal. This alerts the operator who will return to the original blood sample to make a film.

## THE BLOOD FILM

A blood film is simply made by smearing a drop of anticoagulated venous blood onto a glass slide with a glass spreader (Fig. 2a). In larger laboratories film spreading can be automated. Following drying, the film is fixed with methanol and stained. Routine stains are based on *Romanows's method* - commonly used variants are the May-Grunwald- Giemsa (MGG) stain and Wright's stain. Constituent dyes include methylene blue, azure B and eosin. Once stained the blood film should be systematically studied under the light microscope - the normal appearance of a film stained by the MGG method is illustrated in. Alternative stains are sometimes needed. Visualisation of reticulocytes requires the use of a dye such as methylene blue on live unfixed cells ('supravital stain'). Malarial parasites are most easily seen following staining at a specific pH.

The first step in film examination is a decision as to whether the film is of adequate quality. Either poor staining techniques or prolonged storage of the specimen may make the film worthless. Any comment on the film appearance is usually appended to the blood count report. The nomenclature used in film reporting can appear obscure; some more commonly used morphological terms are listed in Table 1.

Where the film is significantly abnormal, examination of the bone marrow can give further diagnostic information.

## BONE MARROW EXAMINATION

The clinical procedure for obtaining samples of bone marrow is described in the other text. From the favored site, the posterior iliac crest, it is possible to obtain both a marrow *aspirate* sample and a marrow *trepbine* biopsy.

### Aspirate

The aspirate is simply sucked through the needle and spread onto a glass slide; the marrow particles are normally easily visible. The marrow is fixed and stained as for a blood film and additionally stained by Perl's method to demonstrate iron. Microscopy and reporting is systematic with reference to the overall cellularity, the appearance and number of each normal cell line, possible infiltration by malignant cells, and any other pathological features. The advantage of the aspirate specimen is that individual cells are well preserved and subtle morphological changes can be detected. The major disadvantage is that the normal architecture of the marrow is lost.

### Trepbine biopsy

The trepbine biopsy is sectioned and normally stained by Romanowsky, and Haematoxylin and Eosin (H and E) methods. Silver impregnation can be used to demonstrate marrow fibrosis and Perl's stain to highlight iron. The trepbine is less good than the aspirate for identifying morphological abnormalities of individual cells but it is better for detecting abnormalities of marrow architecture and infiltration by solid malignancy. The two types of bone marrow sample are thus complementary.

## Laboratory haematology I blood and bone marrow

- Many blood disorders are first suggested by an abnormality in the blood count - particularly in the haemoglobin concentration, total white cell count or the platelet count.
- Automated haematology counters measure haemoglobin concentration and count and size blood cells.
- Where the blood count is abnormal, examination of the blood film often reveals morphological abnormalities undetectable by the automated counter.
- Significant blood abnormalities can be further investigated by examination of the bone marrow - aspirate and trepbine biopsy specimens provide complementary information.

## LABORATORY HAEMATOLOGY II – Coagulation and the acute phase response

### SIMPLE TESTS OF BLOOD COAGULATION

Despite the complexity of haemostasis (P. 12) it is possible to make a general assessment of coagulation with a few relatively simple first-line tests. As an initial screen of haemostatic function the following tests should be combined with a blood count and film to determine platelet number and appearance.

### The prothrombin time (PT)

The test is performed by adding thromboplastin (usually an extract of rabbit brain or lung) to the patient's platelet-poor plasma, warming, and then adding calcium. The time to clot formation is recorded and the PT usually expressed as the ratio of the patient's time to a normal control time. The thromboplastin used should have been calibrated to allow this result to be converted to the International Normalised Ratio (INR) – the ratio which would have been obtained if the International Reference Thromboplastin preparation had been used in the test. The PT is essentially a measure of the efficiency of the extrinsic clotting system (factor VII) in addition to the functioning of factors V, X, prothrombin, and fibrinogen.

### Activated partial thromboplastin time (APTT)

This test is sometimes referred to as the partial thromboplastin time with kaolin (PTTK) or the kaolin cephalin clotting time (KCCT). Patient platelet-poor plasma is combined with contact factors (kaolin, phospholipid) and calcium and the time to clot formation recorded. The test measures the overall efficiency of the intrinsic pathway (i.e. factors VIII, IX, XI, XII) as well as the function of factors X, V, prothrombin and fibrinogen.

### Thrombin time (TT)

Diluted thrombin is added to patient plasma and the clotting time recorded. The test measures the rate at which the conversion of fibrinogen to uncrosslinked fibrin occurs. Thus, the result is affected by quantitative or qualitative abnormalities of fibrinogen and by the presence of inhibitors such as fibrin/fibrinogen degradation products (FDPS) and heparin. In many laboratories the TT as a first-line test has been replaced by *quantitation of plasma fibrinogen*.

Common clinical causes of abnormal first-line coagulation tests are shown in Table 1. Second-line tests may be needed for more precise diagnosis. In *mixing experiments* (or correction tests) patient plasma is mixed with normal or factor-deficient plasma prior to repeating first-line tests. If a particular coagulation factor is thought to be lacking, a quantitative assay can then be performed. A circulating inhibitor of coagulation is suggested by failure of the coagulation abnormality to be corrected by the addition of normal plasma. Many routine tests are now automated. Most coagulation instruments rely on measurement of changes in optical density to detect clot formation.

**Table 1 Common causes of abnormal first-line clotting tests**

Test prolonged	Prothrombine time	APTT	Thrombin time
Common causes	Warfarin	Heparin	DIC
	Liver disease	Haemophilia	Liver disease
	Vit K deficiency	vWD	Heparin
	DIC	DIC	
		Liver disease	
		Lupus anticoagulant	

APTT activated partial thromboplastin time; DIC, disseminated intravascular coagulation; vWD, von Willebrand's disease

### MEASUREMENT OF THE ACUTE PHASE RESPONSE

In assessing patients with ill-defined symptoms it can be helpful to measure activation of the acute phase response, the body's response to tissue damage. Evidence of activation of the acute phase response suggests a physical cause for symptoms.

Possibilities include trauma, infections, neoplasia and autoimmune disease. Serial measurements can be useful in monitoring the effects of treatment. The most widely used measurements of the acute phase response are the erythrocyte sedimentation rate (ESR), the plasma viscosity, and C reactive protein.

### ESR

In this simple and inexpensive test venous blood (in citrate anticoagulant) is drawn up into a vertical tube (Fig. 1) and allowed to stand for one hour. The red cells settle out of suspension and the length of plasma cleared after the hour is measured. The normal values are less than 5 mm/hour in men and less than 7 mm/hour in women, although values of up to 15 mm/hour are not infrequent in those over 60 years old. The test mainly reflects fibrinogen levels but is also influenced by  $\alpha_2$  macroglobulin, immunoglobulins and albumin. These proteins buffer the electrostatic repellent forces on the red cell membrane and allow the cells to come together and form reversible aggregates or rouleaux which fall more quickly through the plasma. The ESR result is affected by the haemoglobin concentration with high values seen in anaemia and low values in polycythaemia. A fresh sample must be processed as the result also changes over time.

### Plasma viscosity

This measurement is another indirect effect of the acute phase response, the result correlating with fibrinogen and immunoglobulin levels. The plasma viscosity has some advantages over the more traditional ESR. The normal range is the same in males and females and the result is also independent of haemoglobin concentration. The sample can be taken from the EDTA anticoagulated blood count bottle and the test does not need to be performed immediately. The normal range, which is temperature dependent, is detailed in Table 2. Plasma viscosity measurement has direct pathophysiological relevance in myeloma where very high values are seen in the *hyperviscosity syndrome*.

**Table 2 Clinical significance of the plasma viscosity**

	Plasma viscosity (mPa.s) 25°C	measured at 37°C
Normal range*	1.50-1.72	1.15-1.35
Acute/chronic organic diseases (malignancy, infection, etc.)	1.75-2.55	1.36-1.99
Need to exclude paraproteinaemias/ hyperviscosity syndrome	> 2.55	> 2.00

\*Slightly higher levels can be seen in normal older people

**Urine electrophoresis.** The highlighted sample proteinuria and the presence of Bence-Jones (immunoprotein (red oval) in a patient with myeloma and re

**Flow cytometry.** Haematopoietic stem cells labeled with monoclonal antibody to CD34 conjugated to the fluorochrome fluorescein isothiocyanate (FITC). (Courtesy of Coulter Electronics Ltd.)

### C reactive protein (CRP)

This easily measured protein is elevated in most types of tissue injury. The CRP is usually increased within 6-8 hours of the insult. The normal range is up to 2 mg/l with levels of 10-40 mg/l in severe viral infections, levels of 40-200 mgA in bacterial infections and levels over 300 mgA in severe burns. CRP results are not influenced by anaemia.

Other possible measures of the acute phase reaction include quantitation of fibrinogen, haptoglobins, alpha-1-antitrypsin and anti-chymotrypsin. These all rise following tissue damage but some acute phase reactants (notably albumin and transferrin) actually fall.

### ELECTROPHORESIS

Electrophoresis has two routine applications in haematology. In the diagnosis of haemoglobinopathies (e.g. sickle cell anaemia), cellulose acetate electrophoresis at alkaline pH is used to separate the abnormal haemoglobins. Citrate agar electrophoresis at a lower pH may be helpful in selected cases. In the investigation of myeloma, serum and urine electrophoresis is performed to detect the monoclonal immunoglobulin or light chains characteristic of the disease.

### FLOW CYTOMETRY

Flow cytometry is essentially the measurement of the characteristics of cells passing in a fluid stream through a detection apparatus. The automated cell counters described in the previous section are the major application of the flow cytometry principle in haematology but the technique also plays a key role in leukaemia diagnosis. Leukaemic cells often have a particular 'immunophenotype' - a characteristic pattern of detectable antigens on the cell surface and in the cell cytoplasm (see also relevant disease sections). The antigens are identified by *cluster differentiation* (CD) numbers. Cells are incubated with specific CD monoclonal antibodies which are conjugated with a fluorochrome. The flow cytometer is then used to detect populations of cells labelled by the fluorescent marker.

### Laboratory haematology II - coagulation and the acute phase response

- Despite the complexity of haemostasis the coagulation mechanism can be assessed with a few relatively simple 'first-line' tests.
- The term 'acute phase response' describes the body's response to tissue damage; commonly used measures include the ESR, plasma viscosity and C reactive protein.
- Electrophoresis is routinely used in the diagnosis of haemoglobinopathies and in the investigation of myeloma. Flow cytometry methodology is exploited in automated blood cell counters and plays a key role in the characterisation of leukaemia.

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Haematology

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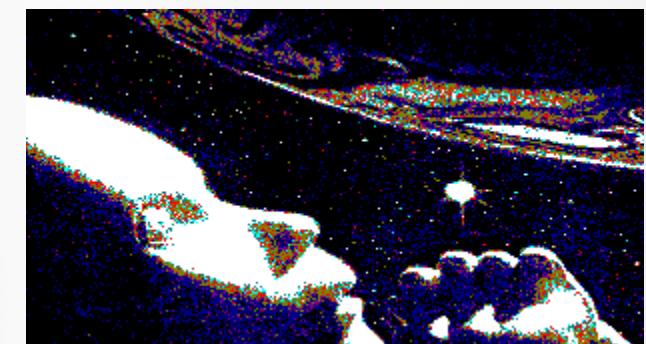
### **Keeping you abreast, Keeping you informed!**

***The Best in Practical Homeopathy...***

***Changing Times, Changing Environments...***

***Allopathy vs Homeopathy***

***Natural + Energetic Medicine***



## **To the Interested Reader**

The fields of natural medicine, homeopathy, and energetic medicine have received much attention in the last few years. The fear of synthetic chemicals, the ecological damage caused by the chemical industry, failure of antibiotics, realization of the chemical special interest groups ability to manipulate medicine, and

an overall developing appreciation of nature, all have brought these forms of medicine into our awareness. Patent synthetic medicine dramatically profits from its synthetic patents, and then tries to get us to believe that the synthetic substance is the same as the natural. More and more people are doubting this.

The vast body of research included in this reference on quantum medicine is dedicated to offering evidence that synthetics are not the same. There are writings on physics, quantum biology, historical accounts and lots of clinical research.

The basic clinical hypothesis is:

### **Can a medical practitioner use natural products in his practice to substitute for the synthetic medications?**

Can a doctor substitute behavioral and homeopathic medicines for synthetic drugs such as synthetic thyroid, NSAID, blood pressure medication, pain killers, antibiotics, antifungals, calmatives, and thousands of synthetic medications on the market today.

This is the basic inquiry we pose. The studies are centered around this hypothesis. The results will definitely point to the conclusion that much of modern medicine indeed can be accomplished with the homeopathics described in these research articles.

Each of these studies is constantly being challenged and retested by our revalidating staff. Each of these articles on its own is not enough for a drug trial yet, but at present there is enough data to conclude that our original hypothesis is correct. We use these techniques in our clinics on a daily basis with greater success than the old style synthetic medications. These studies represent only a smattering of the thousands of successful interventions we see with homeopathy and behavioral medicine.

The basic scientific premise is that nature has many subtle differences that synthetic chemicals do not. There is a measurable and dramatic difference in safety, with natural homeopathic medication having far less side effects.

With these ideas in mind we offer the medical and scientific community the volumes of evidence and research contained in this quantum medicine network.

Read, Enjoy, Learn, And Think.

Yours Truly

N Vilmos M. D.  
Chief Medical Editor

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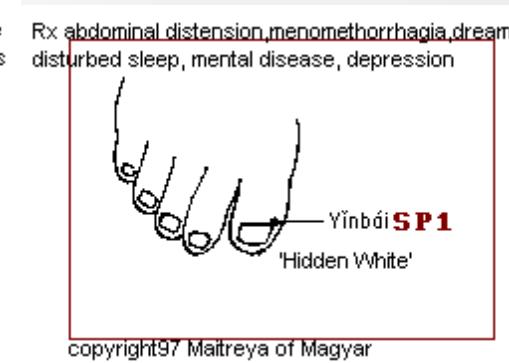
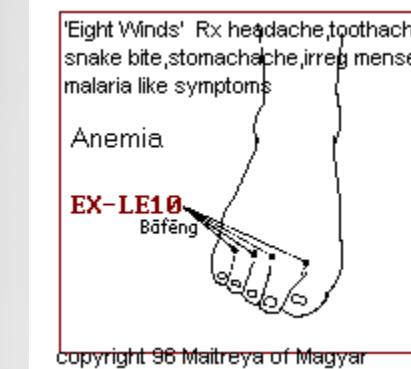
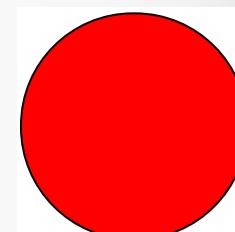
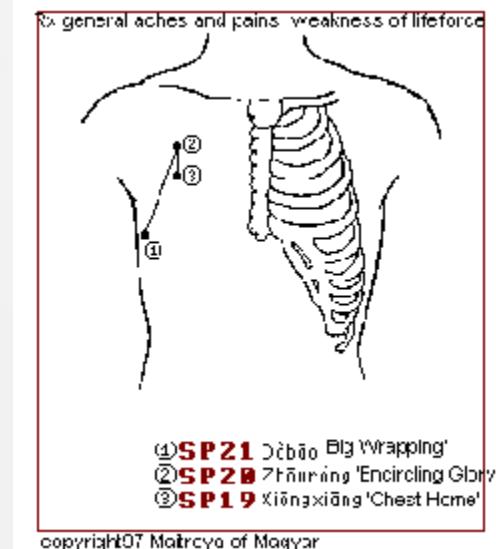
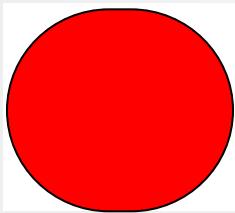
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## ANEMIA

1. Anemia is a condition with many potential causes. Hemolytic anemia results from a deficiency of iron or the inability to activate iron in the blood. Pernicious Anemia comes from the inability of B-12 either from deficiency or activity to activate in the blood cells. Pyridoxal anemia results from a deficiency of B6. Iron toxicity anemia and alcoholic anemia occur from too much accumulation of iron in the body. Megaloblastic anemia results from a deficiency of folic acid and can occur during pregnancy.
2. Anemia can result from a nutritional deficiency and can develop from internal ulcers in the stomach, small intestine, or large intestine which robs blood. Anemia can also occur due to hormonal imbalance and in women during their menstrual cycle.
3. The signs of anemia are low energy states, fatigue, paleness of the skin, a whiteness condition found underneath the eyeballs by pulling down the lower eyelid, pains in the kidney and back, a perpetual tiredness, and the inability to get up in the morning.
4. \*BLOOD LIQUESCENCE has homeopathic, mineral and vitamin compounds to aid in a wide variety of anemic conditions. \*BLOOD LIQUESCENCE puts back into the blood stream the various factors needed to correct anemia as well as to stabilize the energetic factors of anemia.
5. In treating low grade anemia, good nutrition, removing addiction dependencies, reduction of stress and exercise are beneficial.
6. When the body has good healthy white blood cells in adequate numbers, oxygen is transmitted easily from inside the lung into the red blood cells which is then carried to all parts of the body. The measure of health to an organ is how well it uses oxygen. Oxygen is indeed important in the establishment of health and wellness. \*BLOOD LIQUESCENCE helps in the transfer of oxygen into the cells.
7. Another formula which helps in oxygenation is \*HERBAL LIQUID BEE POLLEN which is a blend of herbs, minerals, vitamins, and other compounds that have been well researched for their assistance in oxygenation (ref. Anemia Study and Herbal Liquid Bee Pollen Study).

RED BLOOD CELLS (NEED IRON, FOLIC ACID, B12, ENZYMES ETC)  
Blood liquefaction has all of the factors needed for correction of anemia

Hemoglobin carries oxygen to the cells of the body.



# Haematology

## BLOOD ANALYSIS

As we check the ElectroPhysiologicalReactivity of our patient we soon find that the unconscious reactions can hard to understand. This is particularly true of very sick people. The blood is the most valuable and technically perfect of fluids. thus it is defended greatly by the body. The blood then is one of the last places to detect disease. Heroic modern medicine is designed to deal with crucial diseases and these appear in the blood analysis. In developing the Nelson Method of Medicine we try to get people to see us in the earliest stages of disease. But most of our clients still have deep disease states. So blood analysis is of vital importance.

But the medical system has some loose criteria of what is an improper blood profile. So I have taken my experience and knowledge of blood analysis and applied it to the blood science. So when you input in the value in SI terms you might get a different outcome from others. But we are trying to prevent disease and disease progression. We want to promote healing, cure, and recovery not just symptoms.

The first signs of disease states provide warnings. Any blood change of significance means the disease is already in progression. The results are best done in SI terms but there is a conventional input as well. A list the items and the values are contained in this text. There is also a link to the possible mental states of the patient. The system will reveal a list of possible or probable diseases. You will need to access and rule out which ones are true or not.

## Reference values for Blood (B), Plasma (P), and Serum (S)

TEST	NORMAL ADULT RANGE CONVENTIONAL UNITS	SI UNITS
Blood, Acetoacetate plus acetone(B)	Negative	
Blood, Aldolase (S)	1,0-8,0 u./L	16,6-135 nkat/L*
Blood, Aminotransferase (S)		
Alanine(ALT, SGPT)	5-30 u./L	83-500 nkat/L*
Aspartate (AST, SGOT)	5-25 u./L	83-415 nkat/L*
Blood, Ammonia (B)	11-35 $\mu$ mol/L	11-35 $\mu$ mol/L
Blood, Amylase (S)	60-160 u./dL	111-296 u./L
Blood, Ascorbic acid (B)	0,4-1,5 mg/dL	23-85 $\mu$ mol/L
Blood, Bilirubin (S)		
Direct (Conjugated)	0,1-0,4 mg/dL	1,7-6,8 $\mu$ mol/L
Total	0,3-1,1 mg/dL	5,1-19,0 $\mu$ mol/L
Blood volume	8,5-9,0% of body weigh (kg)	80-85 mL/kg
Blood, Calcium (S)		
Ionized	2,1-2,6 mEq/L	1,05-1,30 mmol/L
Total	4,25-5,25 mg/dL 4,6-5,5 mEq/L 9,2-11,0 mg/dL	2,3-2,75 mmol/L
Blood, Carbamazepine (P)	3-12 $\mu$ g/mL	12,75-51,0 $\mu$ mol/L
Blood, CO2 content (S)	24-30 mEq/L	24-30 mmol/L
Blood, CO (B)	<5% of total Hb	
Blood, Carotenoids (S)	0,5-3,0 $\mu$ g/mL	0,9-5,6 $\mu$ mol/L
Blood, Ceruloplasmin (S)	27-37 mg/dL	1,8-2,5 $\mu$ mol/L
Blood, Chloride (S)	96-106 mEq/L	96-106 mmol/L
Blood, Cholesterol (S)	120-220 mg/dL	3,1-5,68 mmol/L

Blood, CK (S)			
Female	10-70 u./L	166-1167 nkat/L*	17-42 $\mu$ mol/L
Male	25-90 u./L	416-1500 nkat/L*	>68 $\mu$ mol/L
Blood, CK isoenzymes (S)	5% MB or less		
Blood, Copper (S)	70-155 $\mu$ g/dL	11-24 $\mu$ mol/L	60-80 gm/L
Blood, Creatinine (S)	<1,5 mg/dL	<133 $\mu$ mol/L	35-55 gm/L
Blood, Digoxin (S)			20-35 gm/L
Therapeutic	0,8-2,0 ng/mL	1,0-2,6 nmol/L	
Toxic	>2,5 ng/mL	>3,2 nmol/L	1-4 gm/L
Blood, Ethanol (B)	Negative		4-11 gm/L
Blood, Glucose, fasting (P)	75-105 mg/dL	4,2-5,8 mmol/L	5-16 gm/L
Blood, Iron (S)			5-14 gm/L
Total	50-150 $\mu$ g/dL	9-27 $\mu$ mol/L	0,03-0,10 mmol/L
Binding capacity	250-410 $\mu$ g/dL	45-73 $\mu$ mol/L	3,7-12,3 $\mu$ mol/L
Blood, Lactate (B)			>30 $\mu$ mol/L
Venous	4,5-20 mg/dL	0,5-2,2 mmol/L	
Arterial	4,5-14,4 mg/dL	0,5-1,6 mmol/L	
Blood, Lactic dehydrogenase (S)	50-115 u./L	833-1917 nkat/L*	
Blood, Lead (B)	0-50 $\mu$ g/dL	0-2,4 $\mu$ mol/L	
Blood, Lipase (S)	0-1,5 u. (Cherry-Crandall)	0-1,5 u. (Cherry-Crandall)	
Blood, Lithium (S)			
Therapeutic	0,5-1,4 mEq/L	0,5-1,4 mmol/L	
Toxic	2,0 mEq/L	>2,0 mmol/L	
Blood, Magnesium (S)	1,3-2,1 mEq/L	0,7-1,1 mmol/L	
	1,8-3,0 mg/dL		
Blood, 5' - Nucleotidase (S)	1-12 u./L	16,6-200 nkat/L*	
Blood, Osmolality (S)	280-295 mOsm/kg serum water	280-295 mmol/kg serum water	
Blood, Oxigen saturation (B)			
Arterial	96-100%	0,96-1,00	
Blood, Pco2 (B)	35-45 mm Hg	4,7-6,0 kPa	
Blood, pH (B)	7,35-7,45	7,35-7,45	
Blood, Po2 (B)	75-100 mm Hg	10,0-13,3 kPa	
Blood, Phenobarbital (S)			
Therapeutic	15-50 $\mu$ g/mL	65-215 $\mu$ mol/L	
Toxic	>50 $\mu$ g/mL	>215 $\mu$ mol/L	
Blood, Phenytoin (S)			
Therapeutic	5-20 g/mL	20-79 mol/L	
Toxic	>20 g/mL	>79 mol/L	
Blood, Phosphatase, acid (S)	0,2-1,8 IU/L	3,3-30 nkat/L*	
Blood, Phosphatase, alkaline (S)	23-71 IU/L	383-1185 nkat/L*	
Blood, Phosphorus, inorganic (S)	3-4,5 mg/dL	1,0-1,5 mmol/L	
	1-1,5 mEq/L		
Blood, Potassium (S)	3,5-5,0 mEq/L	3,5-5,0 mmol/L	
Blood, Primidone (S)			
Therapeutic	5-12 $\mu$ g/mL	23-55 $\mu$ mol/L	
Toxic	>15 $\mu$ g/mL	>69 $\mu$ mol/L	
Blood, Procainamide (S)			

TEST	CONVENTIONAL UNITS	SI UNITS
Urine, Acetone plus acetoacetate	Negative	
Urine, Amylase	1-17 u./h	1-17 u./h
Urine, Calcium	<300 mg./day	<7,5 mmol/day
Urine, Catecholamines		
Epinephrine	<10 $\mu$ g/day	
Norepinephrine	<100 $\mu$ g/day	
Urine, Chorionic gonadotropin	Negative	
Urine, Copper	0-50 $\mu$ g/day	0-0,8 $\mu$ mol/day
Urine, Coproporphyrin	30-250 $\mu$ g/day	46-380 nmol/day
Urine, Creatine		
Females	<100 mg/day	<0,76 mmol/day
Males	<40 mg/day	<0,30 mmol/day
Urine, Creatinine	14-26 mg/kg/day	0,12-0,23 mmol/kg/day
Urine, Cystine or cysteine	Negative	

## REFERENCE VALUES FOR URINE NORMAL ADULT RANGE

# the books 3D Views on Natural Cancer Therapies

## Immune Stimulation The True Health Care Debate

Years ago I was excited to see some infomercials about alternative medicine treatments for diseases. The speaker talked a good show and sold me to buy his books. But there was absolutely no real advice in the books, only multilevel companies with more to buy. This made me angry and then I decided to write the best self help books on natural medicine. Editing and collecting the best in real substantiated advice.

Desiré has written two incredible books and made movies to go with them. What to do for influenza and specifically what to do when the next major virus hits. A movie and a self help book designed to really help you and your families understand what to do to protect yourself.

Also cancer is such a devastating disease, and there are ways to help yourself in the kitchen with cooking for cancer patients. Full advice from soup to nuts on exercise, meditation, cooking, and more. Coupled with a video for the science of how it works.

The health care debate is bringing a question of health and care. In this incredible new book Desiré has outlined a very thorough review of the real problems of Health Care. This book will tell you the truth the chemical companies do not want you to hear.



*video goes with the book*



If you need more information on the SCIO and purchase details please get in touch with us

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### 3D Views on Natural Cancer Therapies



#### Immune Stimulation



#### The True Health Care Debate



Urine, Hemoglobin and myoglobin	Negative
Urine, 17 - Hydroxycorticosteroids	2-9 mg/day
Urine, 5 - Hydroxyindoleacetic acid	2-9 mg/day
Urine, 17 - Ketosterois	4-18 mg/day
	<0,08 µg/mL or <120 µg/day
Urine, Lead	0,4-1,3 gm/day
Urine, Phosphorus, inorganic	Negative
Urine, Porphobilinogen	<150 mg/day
Urine, Protein	Negative
Urine, Sugar, quantitative glucose	0,1-0,8 EU/2h
Urine, Urobilinogen	0,5-4,0 EU/day
Urine, Uroporphyrin	<50 µg/day
Urine, Vanillylmandelic acid (VMA)	1-9 mg/day

5,5-25 µmol/day
10-47 µmol/day
14-62 µmol/day
<0,39 µmol/L
13-42 mmol/day
<150 mg/day
0,1-0,8 EU/2h
0,5-4,0 EU/day
<60 nmol/day
5-45 µmol/day

**Hæmatology**

## Changes Inside of RBC Target Cells

C1

Low O2, B12, folic Acid, anemia, insufficient bile, obstructive jaundice Low iron or reduced hemoglobin synthesis, heavy menstruation, ulcers hypothyroidism, spleen dysfunction Dysbiosis, pale skin, lethargy, long airplane travel less than 72 hours, thalassemia, nagging fatigue

Veg. Enzymes, iron, folic acid B6, 12, green foods, liver glandular, HCL taurine, N-Acetyl cysteine, Black, strapmolasses, wheat germ, Kelp, black radish, Pancreatin, choline, Inositol      Mucokehl w/ Alkala Sanuvis

## Inclusions in RBC (Parasitized)

C2

Stressful lifestyle, appear 18-24 months before clinical symptoms, yeast infections, terrain imbalance, pH of saliva acidic dysbiosis, acute and chronic disease skin fungal issues

Stress Management Flora inoculation, 714-X, QXCI Pantothenic acid, propolis B6, Spleen glandular, Vit. A, B6, Mucokehl & Alkala, pH blood 7.35

## RBC appear rough & thorny (Echinocytes)

C3

Increasing dysbiosis, liver spleen issues, impaired O2 delivery

Free radical scavengers, selenium, Raw spleen Liver concentrates, B Complex, PABA, enzymes, Vit. C pH buffered, Vit. E

## 3. RBC Formations

### Rouleau

D1

Hyperviscosity of blood, dysbiosis hyperproteinemia, intestinal stress multiple myeloma, congestion, mental and physical stress, low O2 poor digestion, in asymmetric protein molecules, more serious if mixed with fibrin, mineral deficiencies geopathic, chemical, radiation, stress poor circulation, cold hands and feet

Proper nutrition, flora, pH, Stress if due to Dysbiosis use Mucokehl Latensin, Utilin, Pefrakehl, Sanuvis, HCL niacin, Enzymes, cayenne Trace minerals, B3, pancreatin Drainage of liver, lymph, kidney, Leaky Gut Protocol, calcium lactate pancreas, Tahebo tea, lemon Water, Ozone, DNA Repatterning

### Aggregation

D2

Saturated fat ingestion, Inhibits O2 & CO2 transfer pH and electrolyte and trace minerals and enzyme imbalance, poor excretion ELF/EMF exposure, heavy metals intake of toxic foods, liver issues, long term stress, extreme heat stress, shortness of breath, joint pain, blood pH alkaline Toxic foods, at risk of CVA

Backing soda baths, pectin fermented foods, spiruline, B3, B6, Cayenne EFA, raw foods, HCL & pancreatin Vit. E, Cell food, Celtic Salts Enzymes, Potassium citrate, QXCI flax oil, QXCI, niacin, DNA Repat. Trace minerals, ozone, chelation, Licorice root, organic foods Alkala, & Sanuvis & Nigersan Mucokehl & HCL in IV form

## 4. White Blood Cells Too few

E1

Inadequate immune response, radiation, chemotherapy, free radicals

CBC, Ozone, Blood transfusions, IV Therapies

### White Blood Cells Too many

E1

Infection, digestive issues, look for kloekothecits, allergies, Hodgkin's Leukemia

CBC, Vit C IV, HCL, pH Sanum

### Viability below 75%

E2

Bacterial, fungal, viral infections, Chronic fatigue, smoking, hypoxia, Low HCL, Bit. C and zinc, increase sugar intake, candida, fungus, digestive insufficiency Sugar intake

Raw thymus, grapeseed, Vit. C Ozone therapy & peroxide baths, HCL & pepsin with meals Sanum Candida protocol Super oxide dismutase SOD trace minerals, enzymes

Parasitized WBCs (Enderlein)  
(Eosinophils)

E3

Non seroidal drugs, hypoxia of bowel silver fillings, dysbiosis, leaky gut, leukemia, parasite infection, impaired cellular defense, Hodgkin's more than 1-3% means allergies dark circles under eyes, white spots on finger nails, eczema, fluid retention

Rebas, Latensin, recarcin, Omege testing, for foods, parasites, BTA, Spenglersan test for candida, Vit. A, C B6, Zinc

### Hypersegmented WBC

E4

HCL, B12, folic acid, poor immunity, chemotherapy, chronic deg. Diseases, Malabsorption, glossitis, magenta red tongue, depression, menopausal issues, at risk of heart attack

SOD, mineral analysis for Zinc Copper, manganese, Green Leafy veg. Legumes, spinach, B12, HCL

### Lysing WBC

E5

Immune compromise, cortisone use Lymphatic issue, geopathic stress B12, Folic acid imbalance dental foci, copper pipes, heavy metals assimilation and digestion issues

Enzymes, pH balance  
see viability above  
Omege re heavy metals  
Spenglersan  
5. Fibrin

### Thick Spider web formation

Or bouquets

F1

Dysbiosis, liver kidney stress, Cancer, heart disease, bowel toxicity Oxidative damage in blood, fatigue Arthritis, joint & rheumatic issues connective tissues issues, brain fog, stress to mesenchyme, malabsorption congestion, in O2, flatulence, hypertensive drugs, antibiotics use heart bloating, antihistamine use, headaches, Tylenol use, degenerative & Chronic

diseases Lupus, MS, MG,ALS (tubercolin disorders), alcohol, virus

pH balance, homeopathic drainage, bowel cleanse, EFA, QXCI Spenglersan.,  
Drink water 8 glasses, HCL, vigorous exercise/walks, enzymes, Potassium Citrate Trace minerals, Vit. Bs Mucokehl, Nigersan, & Atox Alkala, Sanuvis, Kambucha tea green foods,

#### 6. Platelets

Platelets not visible with NaCl

2ndary defense readiness impaired

Balance pH, BTA

Aggregation  
G1-G3

PH imbalance, excess protein, toxic foods Triglycerides, stress, cold hands, feet

- O2, inc. chylous material Upward mobility of Mucor (congestor) Diabetes, viral infections including Epstein Barr, Herpes, Hep.C, Angina Niacin & magnesium deficiencies Low consumption of fruits & veggies At risk of CVA, and clots, liver stress  
Poor circulation, high blood pressure Atherosclerosis, degeneration of arterial wall, dec. energy, pain in clvcs When walking, progressive cancer Current EDTA chelation, ozone, H202 causing disease.

Enzyme, digestive support CBC & HDI balance pH, ozone, GIA, DHA, lecithin, omega 3, greens, Vit E & C, raw fresh fats, L-Carnitine, Fish, EFA chelation, N-Acetyl cysteine potassium Magnesium Aspartate, B6, 12 Cayenne, homeopathic drainage, colen cleanse, Doppler, IV of HCL & Mucokehl, chelation Alkala, Mucokehl, Sanuvis, Mucokehl milieu therapy, Enzymes, Milk thistle diet GLA, Lipotropics, Vit C, B6, E, Chromium, Echocardiogram

#### 7. Pleomorphic changes Somatids/Protits

Too few

H1

RBC membrane too thick, does not Allow somatids/Protits to emerge

Too alkaline bloock pH, defense weak

Regulate pH, mineral salts, Viatmins hormones, enzymes, metals

Mucokehl & Nigresan

Too Many = Protit Veil

H1

Acid pH in tissue & alkaline in Blood, During isopathic therapy, Abundance of protons

Blood pH=7.35 for spermit formation Alkala & Sanuvis regulate pH before starting isopathic or other remedies detox kidney of heavy metals

Too Many Chylomicrons Highest 2-6 hrs. after fatty meal, Digestive organ issues

High blood pressure, poor fat digestion, Pancreatic insufficiency, obesity  
Leaky gut, high blood fats, Or liver issues

Fasting blood raw food, liver & spleen concentrate, Vit B & folic acid, Vit. C, lipotropics, homeopathic drainage bowel detox, enzymes, - saturated fats, lecithin EFA

Macrosymprotits (embryonic Bacteria)  
H2

Acid pH in tissue & alkaline in Blood Immune dysfunction, use of antibiotics  
Fermentation digestive process Anaerobic condition, NSAIDS cold hands, feet, poor circulation depression, Myalgias, abdominal pain, cognitive & memory deficits, Leaky gut, inflammatory bowel, enterocolitis, Crohn's, Ankylosing Spondylitis, acne, eczema, psoriasis cystic fibrosis, celiac disease, food \* chemical sensitivities, antibiotic use dental foci = Strp Inf. Environmental illness, flora unbalanced higher Endobiosis,

Alkala & Sanuvis regulate pH, detox liver, Address digestive issues, QXCI for food sensitivities intestinal flora, DNA Repatterning, Notakehl to unlock All B Vits., retinal, ascorbate, tocopherol, zinc, selenium molybdenum, manganese, EFA magnesium, glutamine, Glutathione, flavanoids, figer Spenglersan Mucokehl \* Nigersan or Sankombi

Pterohippen (dry protein)  
H7

Excessive undigested protein in blood related to heart disease, recurrence of disease, asthma arthritis

Enzymes, dietary changes, Nigersan balance pH, raw & green food replace animal protein, Citrokehl Spenglersan, pancreatin, HCL

Yeast Like Forms Naessens CWD (Cell Wall Deficient)

H3

Related to acute & chronic infections can be induced by ultra violet light & penicillin, If pH more and more acidic will develop further resistant to antibiotics & germicides anaerobic terrain, ingest amino acids, Leaky gut syndrome, compromised Intestinal flora, antibiotic therapies Feed on toxins, undigested nucleic acids And lipids, chemicals, high blood sugar  
Colds, earaches, boils

Bio-oxidative therapies, Intestinal flora milieu therapies, propolis Vit. BC,A,B5, 6, & D, Thymus glandular, Zinc, Garlic, Colloidal silver Homeopathic drainage Bowel cleans, olive leaf extract Mucokehl & Alkala, 714 - X, zinc absorption issues, Echinacea

Colloid (transparent balloons) no Nuclei inside, when have 4-7 mychits  
Act as Thrombocytes, & Dendrocytes  
(2nd defense) H4

Regulator of immune response To make sperms, colloids and Macrosymprotits

pH of blood has to be 7.35 QXCI

Thecits with 1-3 or more than 7 Nuclei (Mucor bacteria) called an Ascus (Naessens) is a Thecit with more than 9 nuclei  
H5

Mirros candida, Fermentation process, Leaky Gut, Foci in mouth, chronic disease Cancer, clogged lymph

714-X  
Candida: Colloidal Silver intestinal flora, Utilin, notakehl, w/ Alkala, Ozone, Albicansan, Fortakehl, Dental foci Pefrakehl, Spenglersan, pH balance

Bacterial Rods (higher the Development the more the pathology)  
H6

Virus is a species specific chondrit, Tumors. Dental foci, if in Abdomen can Become Peritonitis, if in the stomach can Become appendicitis, myeloma & Diabetes, muddled thinking

Mucokehl, Alkala, pH balance Oxygen therapies, Zinc, Intestinal flora, Spenglersan, Propolis, thymus, Vit. A,C

Ascits & Synascits (from Mychits)  
May look like flimmering in RBC  
When slide crushed ascits will emerge if present.

H6

Not seen in healthy blood, Even days later, precancerous, Oral pathology, silver, root canals, Bridges, crowns, caps, Alzheimer's, Parkinson's, MS

Needs sperm to copulate with nuclei Mucokehl, pH balancing , Enzymes  
Remove dental foci, Spenglersan

#### 8. Crystals

Hinder circulation to brain & heart Includes heavy metal toxins, White & White-Yellow

Kidney stress, liver stress Sclerotic chunks, inadequate lipase Metabolism, undigested protein  
Inflammatory process, capable of Pleomorphic development, resistant to  
Competitors in environment

Homeopathic drainage, Raw & green food, trace minerals Hydrate body flush the cells Raw liver & spleen concentrate Raw animal & veg. Fats, Vit. Bs, C Folic acid, fiber blend

Yellow-Red Tuberculosis

Enzyme therapies Utilin = drainage Drain/detox kidney Utilin upper body focus  
Notakehl & Nigersan = lower body Spenglersan Liver drainage + Latensin & Taraxecum & Chelidonium Ozone Therapy Nigersan  
Fiber & raw & green foods Colonics, flora replacement digestive enzymes

Trapezoid, broken glass

Steel-Blue with small red rim>>> Tuberculosis  
Brown or Brown-Yellow  
Upper Abdomen, liver, gall bladder

Yellow-Blue-Green >>> Urogenital issues, pre-noplastic stage Tylenol

Blue reflection, Cornflower Blue >>>  
Metabolic Disturbance and/or Aspergillus, Thyroid, pesticides

Red-Yellow >>>Bowel/liver toxicity, constipation, infection, elevated BP. Plaque

Clogged arteries, uric acid, AIS, MS Connective Tissue Disorders TB, Prescription drugs, require change in glasses, skin eruptions, toxic foods, Putrefaction in bowls, leaky gut Chronic Fatigue, Epstein Barr, Herpes, Drug users, cancer, junk food, candida

Square crystals >> Neurological problems

#### 9. Symplasts, Protoplasts>>>

Colloid

Degenerative diseases, toxemia Excess Colloids, nutritional reserves, Toxins, dysregulated Endobiont The harder the symplast the more

QXCI treatments

Thrombocyte & Leukocytes Fibrous Thallus (Naessens)

Pathogenic, High blood alkalinity from Fibrin, release excess amount  
Growth hormone=chronic diseases, Radiation, chemotherapy  
Dissolve w/ Mucokehl & Nigersan &/or Sankombi PH balance, ozone, 714

Protoplasts (grey-white outline) With red crystals

Bacterial & fungal cell with plasma, Membrane, immune compromise, teeth, Dysregulated terrain, urogenital, colds Extreme bowel toxicity, strep. Mutants  
Degenerative condition Fatigue, liver & kidney dysfunction, Breeding ground for bacterial infection  
Vit. B5, 6, A, D, & C Thymus, adrenal & spleen Glandular Zinc, Intestinal flora, Echinacea  
Pancreatin colonics, Spenglersan Mucokehl, Alkala, nigersan

#### 10 Systatogeny

Unification of protein colloids of the Endobiont & different developmental stages, to attain a stable form, of multiple species. Terrain anaerobic, fermentation  
Balance pH , Ozone, QXCI

# Cancer and Live Blood Analysis in DarkField

© By Dr. Hilbert Seeger, M.D., Ph.D., Australia

**T**here are still many practitioners world wide doing live blood analysis in DarkField who claim they can definitely diagnose cancer with this method.<sup>1</sup>

The clinical study: "Erlaubt die Dunkelfeldmikroskopie nach Enderlein die Diagnose von Krebs?" ("Is it possible to diagnose cancer with DarkField microscopy according to Enderlein?") conducted at the University of Giessen/Germany put this claim to rest. Out of 110 patients 12 suffered from advanced cancer. DarkField

microscopy according to Enderlein was carried out by a naturopath with many years of experience in this field. He only managed to diagnose 3 patients correctly.<sup>2</sup>

## Are There Any Real Benefits of Live Blood Analysis with Cancer Patients?

The live blood analysis picture of a cancer patient can really appear quite normal initially. It very much depends on diet, intake of supplements, past and present therapy as well as age and constitution of a patient.

### Examples of initial (first 10 min of blood taking) live blood pictures of cancer patients:



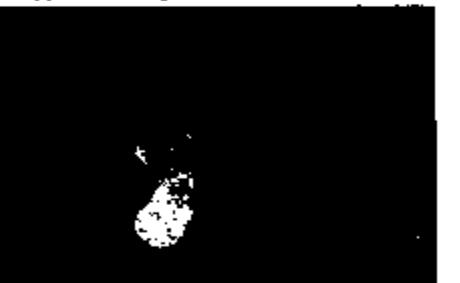
63 year old male, lymphatic metastases, unknown primary cancer, several operations and radiotherapy tablets

62 year old female, breast cancer, partial mastectomy, on Tamoxifen

Both patients stick to an alkaline diet, take the "miracle drink" and supplements

*"Miracle drink"* is water using Alkaline N with whatever the patient needs. (Neo-Samuan, Neo-Citra, Neo-Form, or Neo-San Ger (organic Germanium)).

### Live blood picture of these patients approximately 1 hour later:



Example how intravenous infusions of complementary cancer treatment adjuvants can influence the live blood analysis pictures: 50 year old patient with renal carcinoma, lung metastases, several operations and radiotherapy.

Live blood analysis before



and after infusion



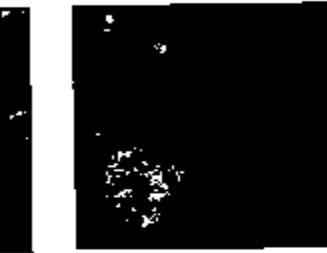
<sup>1</sup> 3. E-Subedić: H.-R. Gudeberg: R. Brückl: R. von Georgi: K. Minsterlin: Klinik für Gynekologie und Geburtshilfe, J. J. Liebig-Universität Giessen, Klinik für Naturheilkunde, Lahmeyer Doctor, Institut für Medizinische Soziologie, J. J. Liebig-Universität Giessen, Deutschland



Live blood appearance after 1 hour at 1000x magnification



Live blood appearance after 2 hours at 1000x magnification

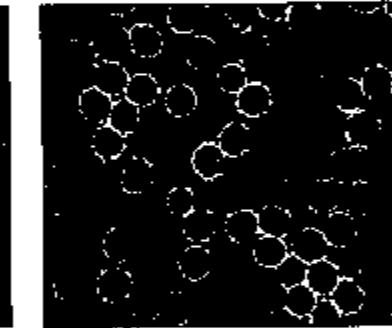


Live blood appearance after 4 hours at 1000x magnification

Examples of live blood analysis of people who feel well and healthy and only had it done out of interest and to see what their blood looks like. Both pictures were taken within the first 10 minutes of taking blood at 1000x magnification.



Experienced dark field examiners see here Leptotrichia buccalis and diplomocci



Even inexperienced examiners see rapid pathological developments here



Many thanks  
R.R. 1  
3626 Fifteen Rd  
St. Louis MO 63114

4. Repeat live blood analysis. There are many factors that can interfere with it. If in doubt, take a new sample and repeat the live blood analysis.
5. Any suspicion of serious developments that may happen in a person need to be investigated by conventional means.
6. Conventional tests reveal nothing but repeat live blood analysis keeps showing highly pathological developments. Start general naturopathic anti-cancer treatment (alkalizing diet, supplements etc) without alarming and frightening the patient.

Correct and professional procedure from here is to advise the patient to have further tests done. I advised the patient of the left picture to see a holistic dentist, because 80% of Leptotrichia buccalis in the blood are due to dental granuloma. To diagnose the right picture as cancer is professionally irresponsible but there are indications that not all is well. First step of further investigations was a conventional blood test.

All examples show how important it is to obey certain criteria for effective judgement of live blood samples and in particular of cancer patients.

1. Good routine and preparation. Slide, cover slide, taking the blood sample.
2. Precise medical and family history, including previous and present treatments, medication, diet, intake of supplements, alternative treatments a.s.o.
3. Initial assessment of the live blood sample within the first 10 minutes. Further assessments after 1 hour, 2 hours and 4 hours. (my guide lines)

We conduct a DarkField microscopy live blood cancer study at present with well over 100 patients to determine how helpful this examination really is. Every case will be documented with DarkField pictures and movie clips. Results of the study will be published on the interactive CD "Live Blood Analysis in Cancer Patients". Planned publication date is July 2008. Please see the advertisement for Dr. Seeger's DarkField Training DVD on page 61 of this issue. ■

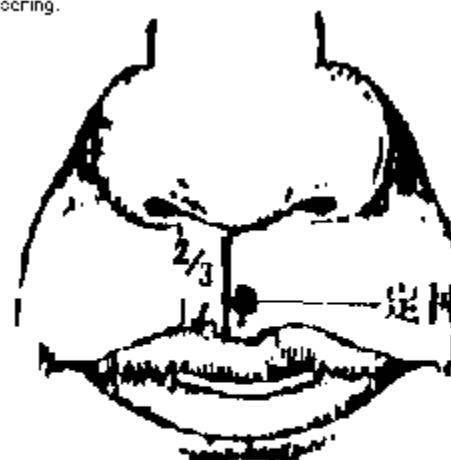
# Haematoiology

## CIRCULATION DISORDERS

1. The body must circulate blood from the arterioles which are rich in oxygen and nutrients to all the parts of the body. The blood then passes through capillaries and recovers toxins and carbon dioxide in the venous function, and brings these back to the pulmonary parts of the heart and lungs to be restored with nutrients and oxygen. In the lung, carbon dioxide is released which can then be expelled.
2. This entire process happens in a cycle of the blood going through the body several times a minute. This overall flow is known as the circulation.
3. Disorders of circulation result in cold extremities, lack of hair growth on the feet and knuckles, poor quality skin and hair, and even a lack of the moon growth on the fingernails of the fingers toward the small fingers. The numbers on form death in the world today is due to some type of circulation disorder. This can result in cardiovascular disease or a host of other types of circulatory disturbances. Problems of circulation to the brain or blockage can result in a stroke or infarction which is also a major killer.
4. The overall flow of blood is usually blocked by stenosis, calcium, build up of plaque or cholesterol, uric acid and oxalic acid, pathogenic compounds, muscular skeletal stress, muscle spasms around muscles of the circulatory arteries and veins, accumulation of thrombosis and platelets, and congealed blood in the circulatory system.
5. \*CIRCULATION is a blend of vitamins, minerals, sarcodes, and venoms designed to help break-up circulatory blockages very slowly. \*CONVALERIA is another product which helps to restore circulation to the brain (ref. Cerebral Ischemia Study).
6. \*CIRCULATION should be taken as follows: 10 drops/2 times per day, for a period of 4 to 6 months to help break-up the circulatory blockage. If the circulatory blockage is broken-up too quickly, this can result in a more severe disturbance. Thus, \*CIRCULATION works on a slow bases to help the circulation to recover slowly (ref. Microvascularity Study).
7. When using \*CIRCULATION we must realize that often times we are going to restore circulation to parts of the body which have not had proper circulation for some time. The body sometimes sequesters toxins or reduces blood flow to an area for its own particular reason. Often times when blood is restored to an area that has not had proper blood flow for some time, this may produce pain or discomfort. Much like blood returns to your arm after having slept on it. At first there is numbness, then after the blood returns it develops some pain. This is usually short-lived, but should be brought to attention.
8. Light exercise is encouraged at first and later building into moderate exercise. Good nutrition along with stress reduction and management is also recommended.

BLOCKAGE FROM CALCIUM BUILD-UP , THROMBOSIS(excess blood clotting after a trauma), PLAQUE , CHOLESTEROL, OR FROM OTHER ARTERIAL BUILD-UP.

This emergency point rests on the upper jaw not the lip. Pressure here can help to revive a person who has fainted. If the person does not respond suspect poisoning.



N-HN-32 (*Dingshen*)

copyright 96 Maitreya of Magyar

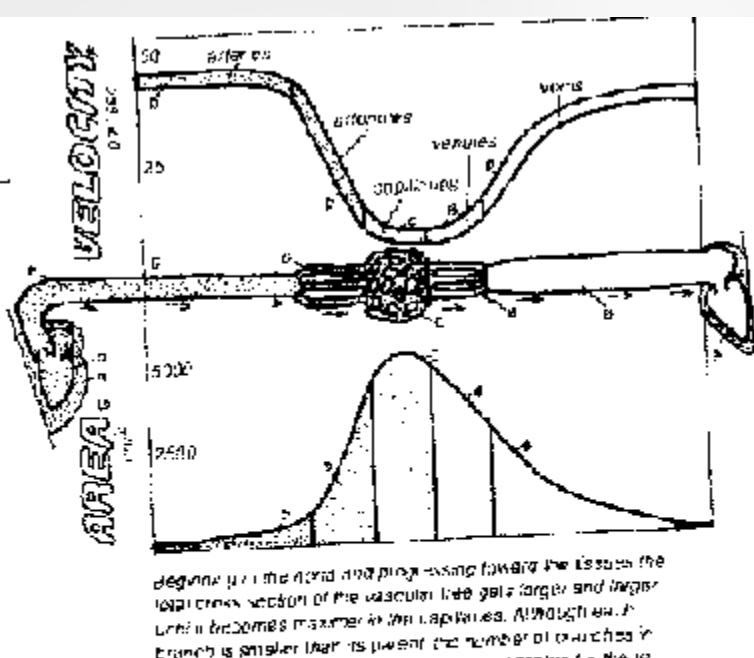


## See Disease First in the Living Blood

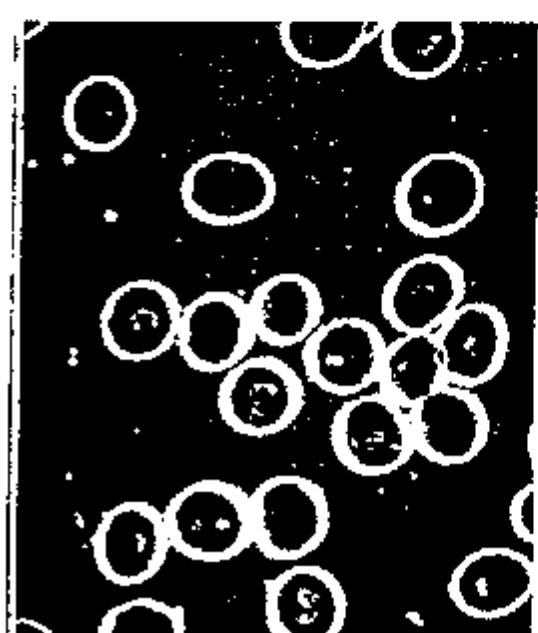
Until recently, scientists assumed that the only diseases generated by microbes were infectious disorders such as AIDS, influenza, or tuberculosis. It was assumed that blood contained no living organisms that could contribute to cancer since the use of standard microscopes had failed to detect any sign of such microbes. When the powerful electron microscope is used, live organisms are placed in a vacuum and subjected to deadening photoplastic changes induced by a barrage of electrons—meaning it is virtually impossible to observe living organisms under an electron microscope.

Based on the findings from more sophisticated light microscopes, there is now compelling evidence that such microbes do exist and may play a major role in cancer. Even better, this advance now enables forward-thinking physicians to see signs of cancer in living blood, even if it is only energetic traces or indications, *before* it manifests as a palpable tumor. French Canadian biologist Gaston Naessens invented an optic microscope called the Somatoscope, which enabled him to view tiny particles in the blood never before seen. He called these particles somatids, which means tiny bodies.

"I have since become convinced that the somatid is the smallest unit of life, the precursor to DNA, capable of transforming energy into matter," Naessens says. What Naessens called "somatids," the German bacteriologist Gunther Enderlein called "proties" and Virginia Livingston Wheeler, M.D., called *Progenitor cryptobionts*. Many researchers believe these are essentially variations of the same microbe. Whatever the name, the research



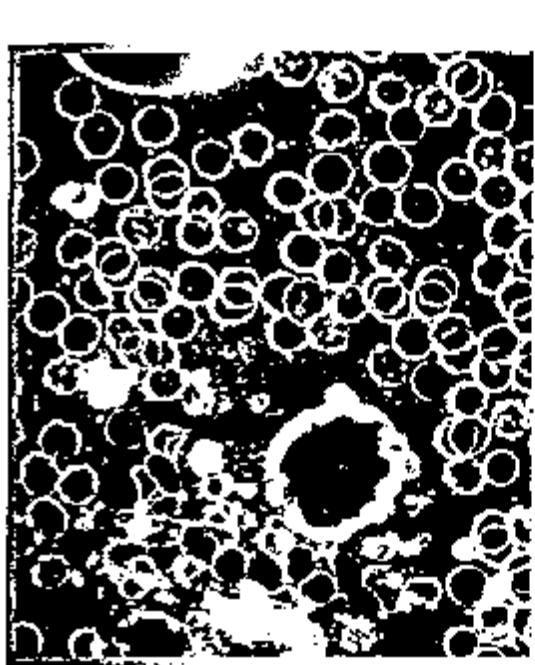
decreasing in the blood and progressing toward the tissues the longitudinal section of the vascular bed gets larger and larger until it becomes maximal in the capillaries. Although each branch is smaller than is given, the number of branches is



Darkfield view of normal blood

cited here tends to confirm the plasmomorphic or form-changing nature of microorganisms believed to underlie the cancer process.

The use of darkfield microscopy was a major change in the diagnostic routine of Maarten Klatte, M.D., a Dutch homeopathic physician and founding director of Vitality Research in The Hague, Netherlands. Like many physicians, he had assumed that all the essential components of blood could be detected by an electron microscope. "Instead of looking at blood, I looked at numbers," Dr. Klatte says. "These



Darkfield view of blood of someone in early stages of cancer

days, I look at the form and motion of the blood components, which include living organisms. I now realize that the old blood analyses, based on measurements, told us relatively little about the true condition of the blood." For Dr. Klatte, the difference between standard blood analysis and the darkfield method is "like the difference between night and day."

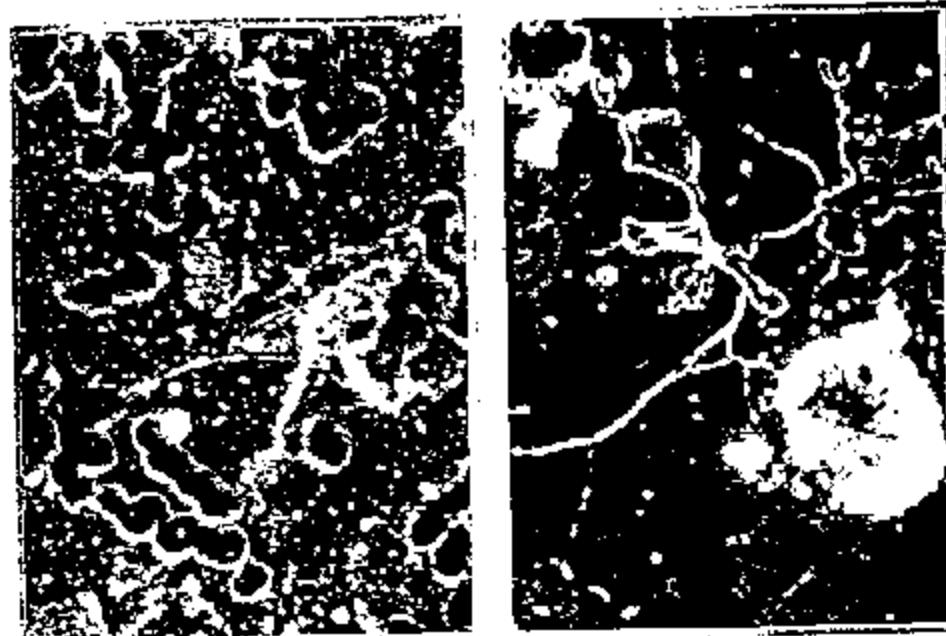
To illustrate the value of the method, Dr. Klatte cites the example of taking the white count of a cancer patient who has come to see him for the first time. The white count is a measure of the concentration of neutrophils (a type of white blood cell) in the

*"When the pleomorphic cycle appears, we can take action and reverse the cycle with therapy," says Dr. Klatte. "If the cycle does not reverse, we know that the therapy is not working."*

blood. The standard procedure is to obtain a total white count and then compare it to the so-called "normal range;" if the patient's white count falls within the normal range, it is presumed to be normal. Using the darkfield microscope, what is normal quantitatively can be abnormal in a qualitative or "functional" sense, says Dr. Klatte. Even though the white cell count in a particular patient is normal, he maintains, the condition of the white blood cells may be revealed by the darkfield microscopy to be far from healthy.

The darkfield microscope enables Dr. Klatte to view neutrophils and describe cells with "ragged" cell walls, cytoplasm leaking out of the cells, and cells that seem immobilized or lifeless. "If most of the cells look paralyzed and broken," says Dr. Klatte, "then the 'normal' cell count means nothing. Motion tells me a lot more about the cells' function. Form tells me whether the cells are damaged by free radicals or whether there are

# Holistic Hematology



Darkfield view of blood of a person with advanced cancer (left) and another with very advanced cancer (right)

## QUICK DEFINITION

Darkfield microscopy is a way of studying living white blood cells under a specially adapted microscope that projects the dynamic image magnified 1500 times onto a video screen. With a darkfield light condenser, images of high contrast are projected, so that the cells appear bright against a dark background. The video physician can detect early signs of disease in the form of microorganisms in the blood stream to produce disease. Blood cells live for about 12 minutes so the amount of time the blood cell stays viable and alive indicates the overall health of the individual. Specifically, darkfield microscopy reveals distortions of red blood cells which in turn indicate nutritional status, possible undesirable bacterial or fungal life forms, and blood ecology patterns indicative of health or illness.

cell-wall) deficiencies that need to be corrected nutritionally." A cell-wall deficiency means that the membrane surrounding the cell is porous or perhaps fragmented, allowing inappropriate or foreign substances to enter and exert harmful effects. Poor cellular function is indicated by a lack of responsiveness to foreign microorganisms.

Dr. Klatte, like many physicians, used to think that in healthy people, the blood and urine are basically sterile. Through the darkfield microscope, he has become aware that the blood is full of living microorganisms. "Thanks to Gaston Naessens, Guenther Enderlein, and others, we now understand much more about the living particles in our blood," says Dr. Klatte, who has worked with Naessens and confirmed the form-changing cycle of Naessens' somatids.

In fact, this cycle reveals the physical states of health and disease, according to Dr. Klatte. The somatid cycle indicates early signs of cancer, usually 6-18 months before the onset of clinical symptoms such as a swollen lymph node or lump in the breast. "When the pleomorphic cycle appears, we can take action and reverse the cycle with therapy. If the cycle does not reverse, we know that the therapy is not working." In the



For more information on the application of darkfield microscopy and pleiomorphic theory to cancer treatment, see Chapter 31, *New Approaches to Immune Surveillance for Reversing Cancer*, pp. 903-909.

physician's hands, the darkfield microscope is an early detection tool and a way to evaluate the effectiveness of a therapy. Dr. Klatte routinely invites his patients to look at their blood before, during, and after treatment. "They now regard their blood as a living part of who they are, rather than as an abstraction, which is the perception they got from viewing numbers [blood measures] instead of seeing blood in its live condition." As the patients watch their blood improve over time, the darkfield images serve as a kind of psychobiological feedback providing positive reinforcement for positive changes.

Douglas Brodie, M.D., a cancer physician profiled in Chapter 3 of this book, makes use of darkfield microscopic principles by way of a simple yet versatile procedure called live blood analysis (LBA). Dr. Brodie uses LBA for obtaining a quick and accurate assessment of his patient's blood composition and viability. With a single sample, taken by a pinprick of the fingertip, LBA is able to provide a composite of numerous factors from living blood.

The darkfield technology allows doctors to observe multiple vitamin and mineral deficiencies, toxicity, and relative degrees of oxygenation as well as tendencies toward liver weakness, excess fat, clotting, and arteriosclerosis. Tendencies toward allergic reactions—including those that may be delayed or hard to determine based on external symptoms—can also be detected using the LBA.

With our increasing awareness of the importance of a strong immune system, the LBA is a valuable tool, providing dynamic assessment of the degrees of cancer resistance a person possesses. LBA permits problems to be detected and treated before more serious complications arise. Physicians can use it to determine blood imbalances that do not show up in the conventional procedure, known as the complete blood count (CBC). "In many cases, the live blood analysis provides information that enables us to predict which direction the cancer patient's body is heading," says Dr. Brodie. "We then make specific adjustments in nutrition and other modalities to optimize the healing process."

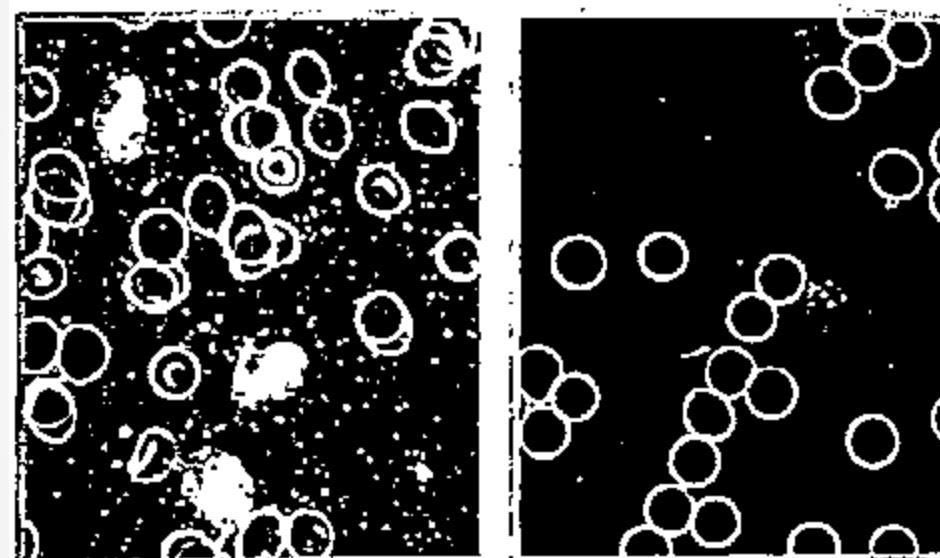
Furthermore, new technological developments enable patients to see the results of their LBA as they are revealed on screen. "I have my patients view their own drop of blood to keep as a reminder to maintain their prescribed nutri-

*Dr. Klatte routinely invites his patients to look at their blood before, during, and after treatment. "They now regard their blood as a living part of who they are." As the patients watch their blood improve over time, the darkfield images serve as a kind of psychobiological feedback providing positive reinforcement for positive changes.*

tional program," says Dr. Brodie. "This is a powerful way to reinforce their own disciplined adherence to the program." The LBA picture also provides a basis for comparison on the next examination; typically, evaluation of the LBA results takes about 20 minutes. Additional lab tests can then be performed to confirm the results and to provide a more comprehensive clinical picture of the individual's condition.



For more information on the Live Blood Analytic system used by Dr. Brodie, contact BioScreen, Inc., 11000 N. University, M.D., Director, 105 North Grandview, Covina, CA 91723, tel. 818-966-7216, FAX 818-966-7226. Dr. Brodie provides detailed instruction materials on darkfield microscopic interpretation and nutritional prescribing to licensed health-care professionals.



Darkfield microscopy photographs of 2 patients—a 49-year-old female suffering from osteoblastic metastasis (left) and a 66-year-old female suffering from primary lung carcinoma (right).

**An Alternative Medicine Definitive Guide to Cancer**  
by W. John Diamond M.D.  
and W. Lee Cowden M.D.  
with Burton Goldberg  
**Future Medicine Publishing Inc.**  
1460 Tiburn Blvd., Suite 2  
Tiburn, CA 94920

## Endobiosis or Blood Parasitism - The Teaching of Prof. G. Enderlein

The history of man is the history of man's errors.

A modern historian has said it, and at no time was this phrase more applicable than for the current situation in our medicine.

After 60 years of impeccable research work, Prof. G. Enderlein has brought forth proof for the CAUSAL origin of all our chronic diseases, including cancer, as well as their successful counteraction.

Prof. Enderlein was a biologist, zoologist, and chief curator of the Zoological Museum in Berlin. He was born 1872 in Leipzig as the son of a family of teachers. He studied the Natural Sciences, especially zoology, and concluded his studies with Promotion *?Summa cum laude.* He was the production manager of the firm SANUM, and founded his own biological Institute where he developed unique preparations out of mould fungi. He died 1968 in Hamburg, at the age of 96, bodily weakened but in full possession of his mental faculties.

Before we enter upon a deeper study of Prof. Enderlein's teaching, we must first provide a brief, historic, overview, in order to make a correct understanding possible. In all of medical history, there has never been a more vigorous and passionate scientific controversy than the one between two French scientists: ANTOINE BECHAMP and LOUIS PASTEUR.

BECHAMP (chemist-biologist and Prof. of Pharmacy-1816/1908) claimed that all animal and plant cells contained tiny granules (he called them *?Microzymas?*), which do not perish at the death of the organism, which are the cause of fermentation, and from which also other microorganisms would arise. These *?Microzymas?*, he said, were in each living body, human, animal, and plants; they are nonperishing and indestructible, and they form the transition between non-living and living matter. Under specific, or pathogenic influences, he said, the *?Microzymas?* could develop themselves into bacteria with putre

factive and fermentative properties. Thus, he said, the diseases had their origin from WITHIN the body. With this, pleomorphism had been discovered and the foundation was laid from which additional research would have developed, if PASTEUR (microbiologist - 1822/1895) had not interrupted this important work. He claimed that all microbes, regardless of their type and species, are unchangeable; that each type would produce only one specific disease; that bacteria and fungi would never arise from spontaneous generation; and that blood and tissues are sterile in healthy conditions. Diseases, he said, have their origin from bacteria that attack the body from the OUTSIDE, and stem from preexisting bacteria.

A third scientist joined in the debate:

CLAUDE BERNARD (physiologist - 1813/1878) corrected: *?No, Gentlemen, the microbe is nothing. The milieu is everything?*

As is known, PASTEUR was very eloquent and effective. Thus he succeeded in convincing the scientific community that he had, indeed, supplied the essential experiments and examination results. Although at that time there were many authors who concerned themselves with the controversy of these two scientists, even accusing Pasteur of using BECHAMP's research in his own works without giving proper credit, the name of PASTEUR is known all over the world, and that of BECHAMP is hardly remembered.

Although PASTEUR is quoted to have said on his deathbed: *?Bernard was correct. The microbe is no-*

thing, the milieu is everything?

Medical thinking had already further developed on the basis of Pasteur's, oversimplification of microbiology, and our current knowledge is based on those partial truths.

Prof. ENDERLEIN entered deeply into BECHAMP'S earlier work and developed it further.

When PASTEUR was 73 and BECHAMP 79, ENDERLEIN was 23. In BECHAMP'S year of death (1908), he was 36 years old; thus he was his contemporary for many long years.

ENDERLEIN HAD ALWAYS CAREFULLY RESPECTED THE RIGHTS OF PRIORITY, as is notable in all of his writings.

ENDERLEIN'S discovery occurred in the year 1916. On the occasion of his work on typhus, he observed in the blood-darkfield tiniest moving beings, which entered into union with higher organized bacteria. Their copulations product became instantly invis

ible. He surmised sexual processes, through which came about, not higher forms (as in embryonal development), but lower forms that were invisible to the eye in the light microscope. These vigorously moving elements had flagella. He named them SPERMITS. Moreover, he had already recognized that in the blood of mammals there was always found a symbiont of plant origin. This organism occurred in diverse forms which, among other things, provided essential functions (thrombocytes) in cases of blood coagulation. Thus, all life corresponded to a *?gigantic primary symbiosis?*, because without the possibility of blood coagulation, there could be no vertebrates.

Healthy life would have to be an Eusymbiosis; correspondingly, diseases would correspond to a disturbed symbiosis. The discovery of the *?Spermits?*, naturally, could not solve all problems, but once the foundation of living forms had been touched, the cycle of microbes in its manifold forms became very quickly describable by Enderlein. He wrote and published over 500 works, most of them about pleomorphism and symbiosis. He spent many years with precise research, examining living blood with a dark-field microscope. This made it possible for him to publish his chief work, BAKTERIEN-CYCLOGENIE (Publisher W. de Gruyter & Co. Berlin, 1925). In it he presented arguments and proofs for pleomorphism, which have to this date remained undefeated.

ENDERLEIN shows in this work that in the *?Struggle for Survival?*, all species strive after balance among themselves; that, by no means, the goal is the elimination of other species through unlimited multiplication, rather the contrary is the case: killing and eating is limited to the unavoidable measure for the maintenance of the species. We allow ENDERLEIN to express himself directly:

*?In 1914, after the First World War began, the medical department of the II.A.K. Allgemeine Krankenhaus (General Hospital) in Stettin, was unable to find a bacteriologist. Therefore, I personally offered my services as a volunteer, in the interest of the soldiers ... Yes, they were very favorably disposed toward me by giving me the rank and income of a staff-doctor although I was in the category of a *?general biologist?* Well, I immediately used these means for the installation of another laboratory in my private household, besides the laboratory in the administrative district of the II.A.K., which was located southwest of Stettin. Then I tried to work at home late at night in order to continue and establish my studies. From my home in northeastern Stettin I rode my bicycle to work in the south western part of Stettin right through town very early in the morning. In this way, I had finished a complete revision of the developmental processes within the bacteria, along with 330*

illustrations, within the span of two years. Because the W. de Gruyter Co. Publishers in Berlin had no intention of printing it during the war, I - seeing its immense significance - began publishing it August 19,

1916, in the *?Sitzungsberichten der Gesellschaft naturforschender Freunde, Berlin, Year 1915?* in the form of a comprehensive abstract with the totality of terms. The identical article became reprinted in the book *?AKMON?, ?Bausteine zur Vollgesundheit und Akmosephie?* Booklet I, 1955 (pps. 68-70). Then also the main work appeared. In that were also large portions of the cycles of the primary symbiont: *?Mucor racemosus Fresen?* described and illustrated in the *?Bakterien-Cyclogenie?*

As early as 1915, I had isolated the endobiont (in the form of the bacterial phases occurring in the blood) out of the blood, and named its pure culture by the valid name *?Mucor racemosus Fresen?*, not calling it by the long antiquated name of *?Leptotrichia buccalis?* (Robin 1879). On the basis of this pure culture, which I cultivated further for decades, (which I had introduced as early as 1915 to an assembly of doctors near Stettin, as well as to the Director, Dr. med. Gehrcke) - the entire series of the development stages had already been laid down in the illustrations prepared for the *?Bakterien-Cyclogenie?* whereby, for the first time, a document absolutely contrary to the general opinion regarding the *?sterility?* of the blood, has been brought forth and fixated ...?

Thus, ENDERLEIN in: *?Folia isopathica?* Vol. I, 1961. Preface by President of the Senat, Dr. jur. Edmund Hegel, Berlin.

And further. In *?Immunobiologica?* Vol. I, pamphlet ?, 1950: *?On the Disease Complex of Endobiosis?*: *?In contrast to the manifold occasional illnesses of man, which are caused by specific pathogens, such as e.g. Micrococcus catarrhalis, Bacillus influenza, Treponema syphiliticum, Pneumococcus, etc. man has two parasitic microbes, which must be understood as the steady companions of his species. More than that, these two parasites stand in a determined relationship to each other; they complement and replace each other mutually. First we want to name the Tubercle Bacillus, which has undergone a series of developmental stages within the human body, on which one or the other of the tuberculous diseases are based upon. In its primitive stage - protit and chondrit - it is already transferred diaplacentally into the embryo ... ?*

...?In a biologically and functionally inseparable relationship to Koch's bacillus, there is an even more dangerous parasite in the human species, which I have named the ENDOBIONT. For millions of years

past, the entire mammal family became infected with a fungus - *?Mucor racemosus Fresen?*. ... Thus, the Endobiont is constantly present in the animal body and neither can, nor should it ever be removed; BUT THE ENTIRE FOCAL ATTACK AND, WITH IT, ALSO THE RELEVANT CLINICAL FORM OF DISEASE, DEPENDS ON THE CONDITIONS OF ITS DEVELOPMENT. This fungal parasite unfolds all stages of its total development within the body and can attack all tissues and organs, more or less.

Exactly this fact is what makes the Endobiont so dangerous for the human being, and precisely this circumstance has the consequence of the entirely unusual manifoldness of the focal attack. According to statements of A. Leschke, already the ovum and sperm are attacked, in contrast to Tuberculosis, where an infection has to occur...?

?... The Endobiont usually occurs as carcinoma, and the Koch Bacillus as lung tuberculosis. But both parasites may also occur in most of the other diseases, especially in their chondrit stage. Therefore, the treatment must take this into account, because the diagnostic delineation of the attack is not possible, particularly in the primitive stage. Thus, a combination treatment is a necessity from the beginning. The hydrogen-ion-concentration (pH) of the blood gets shifted through the Endobiont, whereby it must be especially emphasized that the Endobiont expressly devours protein. It is understandable that these facts create ever enlarging preconditions for the endlessly ongoing development of the Endobiont.

A. LESCHKE made a significant discovery, and proved, that the ferments of the turtle -bacillus (Sclerothrix antituberculosis Enderlein = Utilin *?S?*, was further developed into todays remedy out of Mycobacterium

phlei) are able to absorb and, thereby, neutralize the ferments of the Endobiont. Thereby, the shifted pH gets restored. This fact forms the unavoidable precondition for every successful treatment, both antiendobiontically as also specifically. ?

In summary, we can say that the researches of Prof. Enderlein have revealed:

1. The cell is not the smallest living unit, but the colloid is

(Colloids are particles of a size under 0,2 pm, which means, they remain below visibility under the light-microscope, but they lie distinctly above the molecular measurements of low-molecular substances. In image-comparison: 100.000 of them laid side-by-side measure 1 mm). cf. *?Das Ende der Herrschaft der Zelle als letzte biologische Einheit?* (G. Enderlein, in: *Archiv fur Entwicklungsgeschichte der Bakterien*. Vol.1, pamphlet 2, July 1933 Pg. 171179. 5 Illustrations).

2. The proof that bacteria have a nucleus or nucleic equivalent (Myth)

This understanding has been seriously opposed by the teaching opinion of his day, however, barely 20 years later it became confirmed (Harmsen) through the development of the phase-contrast and the electron microscope.

3. Proof of the sexual propagation of bacteria Enderlein clearly differentiates in all microbes between sexual and nonsexual propagation; between the formation of larger microbial forms (increase in valence) of the PROBAENOGENY, and pure increase by numbers of AUXANOGENY. The nonsexual propagation occurs by sprouting and splitting, the sexual is connected with a copulation or nucleic fusion. The sexual propagation has been confirmed by the researches of Nobel-Price recipient J. LEDERBERG and EL-TAUMG, USA, and Prof. W. Hayes, Edingburg - 40 years later! - although, without mentioning the research of ENDERLEIN.

4. The scientific proof and foundation of pleomorphism in microbes

This teaching reveals that a certain type of microbes can occur in diverse forms and developmental stages under precisely established conditions, beginning from the smallest grades of ultramicroscopic magnitudes up to the large, multinucleic, highly-developed stages of bacteria and fungi. Enderlein started from the observation that, the further one goes back in the development - from the highly developed and complicated to the simple - the more plastic and changeable get the life substances and the faster do the life forms merge into each other, due to the changes in the living conditions.

Enderlein was able to proof this after long and tedious research works. The result of his labor is the work titled *?Bakterien-Cyclogenie?* (from the greek *?kyklos?* = circle and *?genos?* = birth, origin). It shows the developmental course of bacteria from the tiniest virus stage of the protein-like tiny lump, up to the stage of bacilli, and from here, to the microscopic fungal stage.

All this has been confirmed through research done in more recent years, especially by the Tuberculosis-Research-Institute in Borstel, by KOLBEL, G. DOMAGK, UYEDA, H. HARMSEN and G. MEINECKE. As usual, many of these reports failed to refer to ENDERLEIN.

5. The proof that there is no sterile, germfree blood

Enderlein says that in the serum of all people and warm-blooded animals there are living microorganisms. He called them ENDOBIONTS (from the Greek *?endon?* = internal and *?bios?* = life). 40 years later, other authors named them *?Microsomes?* or *?Chondriosomes?* without consideration of ENDER-

LEIN's priority, and they claimed that they are endogenous elements of the blood. But, the research by ENDERLEIN revealed that there is a developmental form of the Endobiont which is of a plant nature. He called it THECIT, and recognized them to be entirely identical with the Thrombocytes. That occurred already in 1939 (cf. Microbiological Congress, USA) and afterwards came the news from the USA that the ferments of the Thrombocytes have been found to be entirely different from those of human cells. In most recent times, it has also become confirmed that English researchers have certified plant enzymes on Thrombocytes, although - again - without mentioning ENDERLEIN's research.

The human being lives in symbiosis with a plant microorganism, the ENDOBIONT.

There is no human being who has not diaplacentally acquired this Endobiont and has not hosted, at the least, its primitive stages in his own cells and body fluids his whole life long. They are even in the sperm and the ovum.

Within the developmental series of the Endobiont, the lower phases (Protit, Protit, and Chondrit) are apathogenic and are therapeutically usable. All other higher forms can facilitate or produce diseases, whereby they penetrate, not only the blood cells, but also beginning from various stages-the cells of tissues to influence them degeneratively.

In their multiplication, the primary tiny lumps begin to differentiate themselves and they appear in unimaginable numbers of diverse forms. Of these, certain ones - especially those getting abundant supplies of animal protein - increase in size, get a small spherical form, with a nucleus residing at the cellwall. Through division it becomes the source of a micrococcus with two nuclei. From them, bacteria with 4 - 8 nuclei develop, and finally a bacillus with 16 and more nuclei. Here, we have the progenitors of the masses of bacteria and bacilli, which we develop in ourselves, according to Enderlein.

During further development, there suddenly arises in the midst of this assembly a formation, in which the nuclei are grouped in an irregular fashion, either across or obliquely to the length-axis, or else parallel to it. It will later on become the ancestors? of the large group of microscopic fungi, in which a central canal with solid walls forms inside the body. There masses of primary nuclei gather, in order to become expelled as primitive forms for the purpose of propagation. Thereby, the large cycle the Cyclogeny - from the primary stage of the tiny protein lump, via the bacterial and bacilli stages, up to the fungal stage with its enormous productivity of primitive forms, is ended. But what is it that makes these tiny primary clumps of protein into such rabid beasts that makes them turn against the cells of its hosting organism (the human being or mammal)? Our civilization causes or facilitates the upward development through artificial fertilizers, preservatives, coloring substances, air pollution, etc., but in the very first place stands our false nutrition, which literally ?fattens? the Endobiont by its high-content in protein and sugar.

So ENDERLEIN says: ... ?As soon as the balance of the blood serum between mineral salts (bases, alkali) and acids has become disturbed toward the acidic side through long-continued, antibiological nutrition, a limitless proliferation of this Endobiont begins, and simultaneously, the rise of these tiny primary lumps which now become parasites, via an extensive, developmental series. The higher this Endobiont rises within its developmental series, the more its harmfulness increases, and the higher rises the over-acidification of the blood; both standing in a mutually aggravating interrelation.?

According to ENDERLEIN, all chronic diseases are based on this development into higher forms of the Endobiont. The higher valenced forms are parasites. They will then develop their own metabolism that poisons the human bodyfluid (predominantly by high-grade rise in lactic acid production). He says:

?Basically, there is not a multitude of diseases, but only one constitutional disease, namely the constant over-acidification of the blood, which disturbs the central regulation of the human body, disorienting it, all of

which is mainly the result of an inverted way of living and eating?... ?It is chiefly the current, civilized food with its abundance of animal protein, especially meat, fish, and eggs, which causes this over-acidification, on the one hand, and masts the parasites, on the other hand. Therefore, a lacto-vegetarian food is the biologically and nutritional-physiologically correct nutrition, because it lowers the over-acidification by its abundance of bases and alkaline salts. If it is used from childhood on, or better yet, used by the mother before the marriage - it can prevent and heal all diseases.?

By the upward development of the endobiont, a decrease of the regulatory equilibrium in the interchanging relationship with the vegetative centers in the diencephalon occurs, which leads to a failure in its shape and forming function.

6. Disease means symbiotic disturbance Whether by simple expansion or increase in numbers, the Endobiont spreads in the body of man and warm-blooded animals and its higher developmental forms congest the circulatory system (prethrombosis, thrombus of the capillaries, etc.)

7. The symbiotic disturbance

It is recognized in the darkfield by the ABSENCE OF CERTAIN GROWTH FORMS OF THE ENDOBIONT (Diokothecits). As bioregulators, these maintain the balance in the symbiosis. Simultaneously, diverse pathogenic cellular elements occur.

8. Symbiotic balance

The healing of diseases is possible only when the body regains the lost regulators. That is, the primitive-apathogenic developmental forms (Chondrits) which metabolize the higher, parasitic developmental forms through copulation with them, so that they subsequently leave the body through the organs of elimination (kidney, intestine, lung, skin).

9. The questions regarding health concern living processes exclusively

Therefore, they can be resolved only through the BIOLOGICAL science.

In conclusion, a brief report on:

The mutually positive performances of the two associates in the primary symbiosis: MAN and ENDOBIONT

I. Associate: MUCOR RACEMOSUS FRESEN, the ENDOBIONT:

1. Formation of DIOEKOTHECITS for the establishment of regulators in two directions, both with extreme mobility.

1.1. SPERMITS for the degradation of its own higher and pathogenic developmental phases.

1.2. Formation of MICROSYMPROTITS for the degradation of higher and pathogenic phases.

2. Formation of COLLOIDAL THECITS for the production of REGULATORS in one direction.

2.1. Extremely mobile MICROSYMPROTITS for the degradation of higher and pathogenic phases.

3. Formation of THROMBOCYTES.

3.1. For the production of SPERMITS acc. to Enderlein, 1916; valid name, with priority over: BAKTERIOPHAGES, a synonymous term that has been brought in by d?Herelle in 1917, which is invalid and fundamentally wrong. Both relate to the characteristic memory within the identical microbe.

3.1.1. Through formation from outside by their tie-offs 3.1.2. Through symplasm (agglutination) of the same into larger, and up to very large, heaps, which subsequently expell their entire contents inwardly, along with the micromych (primary nuclei), from which subsequently SPERMITS will arise;

3.2. for the quickly required closing up of wounds. 4. Through the start of SYSTATOGENY of degradation products by COLLOIDS, which stand ready for the building of PSEUDOCRYSTALS, in case of over nutrition, especially with meat and fish. These living colloids from sputum and also from the blood travel - on the slide-smears - within a few minutes, toward the outside parameter of the slide (up to about 5 cm distance) and gradually construct themselves into the forms of limitless pseudocrystals right before your eyes. This process can very easily be observed.

5. Through the formation of SCLEROSYMPROTITTHECITS the fattening of the primary symbiont into sclerotic pseudocrystals is accomplished, that is, kept from developing into higher, pathogenic phases by overeating. However, the sclerotic pseudocrystals cause extremely serious congestive diseases. These sclerotic formations (scirrhotic forms) occur in two different ways:

5.1. Directly to

5.2. Through the formation of SCLEROTHECITS, which develop further into SCLEROSYMPROTITTHECITS and, finally, their total content re-shapes into PSEUDOCRYSTAL FORMATIONS out of colloidal and up to chondrit material, thereby developing into SCLEROSYMPROTITSYMPLASTS.

II. THE HUMAN BEING, HOMO SAPIENS...! What else but a constant decline could be expected as the consequence to centuries of disrespecting the natural biological laws (by a diet that masts the Endobionts, by breakfast decadence, preservatives - culture, and so on). Instinct and Intuition have been lost. Moreover, due to Mercury-Silver amalgam fillings, the chances for a cancerous disease have increased dramatically.

6. All the phantasies built up around MUTATION or even ATAVISM and PROGONISM - such as the one by Max Westenhofer (1907) and Friedrich Faber, ?Cancer, Its Law and Its Secret? (E. Wancura Publishers, Vienna/Stuttgart 1954) are without any biological basis and thus, eliminate themselves simply by the fact that we are here not dealing with protozoa in the endobiont, but that it presents a distinct BACTERIUM-FUNGUS-ORGANISM. It is grotesque to ascribe to the vertebrates an Atavism back to primitive plants! Such things are nowadays covered by the term ?SCIENCE?!

7. LIVER and GALLBLADDER DAMAGES are the sure consequence of mercury or other heavy metals only occasionally caused by cancer, although mercury often enough can lead to cancer in the end.

8. The CAUSAL ORIGIN for the FIRST MANIFESTATION has not yet become known, due to the extreme smallness of LIVING COLLOID (or better, the PROTITIT PHASE), with a diameter of 0.01 pm (= 1/100000 mm).

9. Friedrich FABER, ?Cancer and Its Law? (E. Wancura Publishers, Vienna/Stuttgart, 1984) says on page 297: ?Humanity will be relieved of cancer only when the pioneering, decisive world-changes from the mechanocentric to the BIOCENTRIC AGE will actually come about.? Well, the ?BAKTERIEN-CYCLOGENIE? has been pioneered and AKMON I and II actually already present the solution for the

€

cell phones  
do affect  
the brain

can help a little  
BUT

SCIO

The SCIO can undo the damage by regulating and  
balancing the  
Body Electric's Regulatory Processes  
+ increasing VARHOP

If you need more information on the SCIO and purchase details please get in touch with us  
Maitreya Kft.  
tel: +3613036043 | web: www.qxsubspace.com | e-mail: info@qxsubspace.com

?BIOCENTRIC AGE ?.

As clearly presented above, the ENDOBIONT has applied itself CONSCIOUSLY for hundreds of millions of years to services in favour of the mutual symbiotic association. They were exclusively subordinated to the goal of maximally eliminating the formation of higher and highest - and simultaneously also, pathogenic up to highest pathogenic - phases in most diversified directions. Yet, the mutual associate in the primary symbiosis, the ?HUMAN BEING?, is to this very day without the smallest inkling of this association!

Aside from constantly supplying nourishment, the side of the service from THE HUMAN BEING REMAINS A HUGE ZERO, corresponding to such an exorbitant anaphysm toward the laws of nature. All that is left is his pocketing the final bill from biological natural laws!

### III. OR DOES ANYONE BELIEVE THAT LOGICAL THINKING IS A PROFESSIONAL DISTURBANCE?

Already Pythagoras (582-507, B.C.) has uttered: ?that the gods are innocent concerning the sufferings, and that all diseases and pains of the body are the products of extravagances.?

According to: Jamblichos from Chalkis (3<sup>rd</sup> Cent A.C. in ?The Life of Pythagoras.?

In conclusion, I wish to call attention to the following. The ISOTHERAPY, its remedies being manufactured and marketed by the firm SANUM-KEHLBECK, is based on the discovery of Prof. ENDERLEIN that certain organisms existing in the blood can be developed retrograde, that is, they can be changed back into primitive forms through identical microorganisms. When we apply this biological phenomenon, it is possible to reduce the aggressive activities of the microorganism in the human body, yes, even to make it harmless for the tissue. In other words: We are dealing with the CHANGE OF PATHOGENIC MICROORGANISMS INTO THEIR APATHOGENIC PRIMITIVE FORMS, which then lose interest in parasitism and leave the body through the epithelia, the intestines, the kidney or the bronchial tract.

These remedies are those produced by SANUMKEHLBECK of Germany in consistent continuation of the teaching and direct inheritance from Prof. ENDERLEIN.

Darkfield Seminar

The Growth Forms

of Microbes in the Blood

One cannot fight an unknown enemy! Because a victory over the primary enemy of the human species is only then possible when one knows this enemy, the fundamental need is to specify, first of all, the comparative-morphological and biological developmental foundations, which facilitate our approach in getting to know this entirely unknown and unrecognized primary enemy of the human species. According to Professor Enderlein, pleomorphistically considered, all microbes partake in a natural developmental cycle, that begins with the PRIMITIVE PHASE, which is microscopically invisible or visible with difficulty; this changes into the BACTERIAL PHASE, and finally culminates in the FUNGAL PHASE. This final form of its developmental ascent is its CULMINATION: The fungal culmination can also be replaced by a YEAST-CULMINATION.

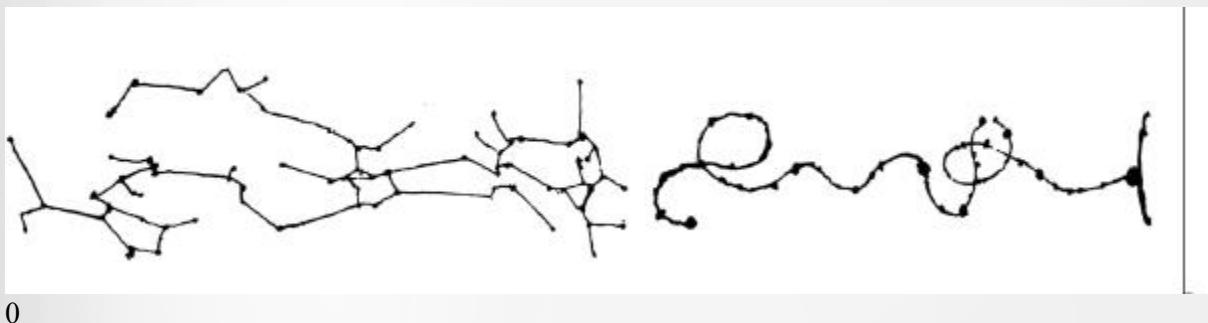
The bacterial stages, however, occurring in between the two extreme phases, are universal and natural for most bacteria and fungi.

Fundamentally, the microbial forms consist in their primitive stages of a homogenous, unorganized, un-moving, yet living protein in colloidal form, which neither includes lipoids nor nucleic acid derivatives as reserves, nor does it deposit them around itself. These purely colloidal proteins have a trillion (that is a 1 with 18 zeros) diversities, which are capable of combining themselves with all elements, even with heavy metals, as well as with nearly all other chemical compounds, right in the human body. From this result huge astronomical numbers of colloidal compounds, which we can grasp at first only in summarized groups.

The most primitive developmental form of every microbe is the PROTIT, the primary biological unit which is pure colloid, with a diameter of 0.01 gm. This is the primary living form in general, on no account a cell (see: ?Das Ende der Herrschaft der Zelle als letzte biologische Einheit?: G. Enderlein, im Archiv für Entwicklungsgeschichte der Bakterien. Vol. I H. 2, July 1933, pps. 171-179, 5 DRAWINGS).

A nationalization (unification) of a number of protits can occur in three ways:

1. A one-dimensional arrangement. This results in a shorter or longer thread, the FILUM; its diameter is that of the protit, namely 0.01 Im. However, it can constantly increase in thickness, after its formation.
2. A two-dimensional arrangement of the protits, like in the spore-heads (= one protit/one filum).
3. A three-dimensional arrangement, namely into more or less tiny granules, the SYMPROTIT.



Endobiont Chondrit-Stadium in Blut. Erythrocyt, auf dem der Chondritflocken fußt. Da viel Symprotite, sehr stark beweglich.

Endobiont chondrit-stage in blood erythrocyte with chondrit - flake being based on it. Since many Symprotits, very mobile.

In the new formation of filum and symprotit, atomicphysical and quantum-biological factors play a decisive role. That is visible from the sudden occurrences by the leap of these new formations (?Quanten-biologische and quantenphysikalische Funktionen der kolloidalen Eiweißelemente der Primitivstadien der

Mikroben (Protit and Chondrit)? in *?IMMUNOBIOLOGICA?* Vol. I, ? July 1950). The formation process of a filum with a head, the SYMPROTIT, occurs within the smallest fraction of a second, which is therefore not observable by the eye looking through the microscope; the new developmental forms simply are suddenly there. A special technique for recognizing these developmental processes is to be used.

These were the growth forms of the primitive phases. Each higher developmental step represents the nationalization of these growth forms just described. In this way, the symprotit uses the protit, namely a colloid, for its advancement, depositing it at first in large numbers right on its surface as nutritional reserves. This reserved living, protein colloid grows ever larger, surrounding the symprotit sphere more and more. By this process, the first cell has come to be, which is a spherical primary cell, the bacterial cell, the MYCHIT. By this process, the symprotit became the primary nucleus, the MYCH, and from the reserve material collection of living colloids came the CELLPLASMA of the primary cell, the Mychit.



#### Bacterial forms of the endobionts.

Development of a mychit (primary cell) out of symprotit, the latter develops into a mych (primary nucleus).

#### **Sclerotrix tuberculosis**

Koch 1882, primary cells (mychits) and transitions into free symprotit. Nonacid-fast form. Enlargement 10 000 : 1.

Further development of the primary cell consists of the increase of valence of the nucleus into a larger, multi-valenced nucleus, that is the cell, the CYSTIT, which has the valence of two or more nuclei.

The THECIT, which is also spherical, comes about from the splitting of the nucleus into two or several nuclei. Actually, the THECIT represents the primary form of the bacterial cell, in which the natural primary type of the sphere has not yet evolved into a bacterial rod through the stretching factor. It can grow into a very large sphere, whereby the nuclei can form themselves smaller or larger. However, they also occur in tiniest forms, near the size of the colloid, and as such, they fill the THECIT in large masses within the primary cell plasma.

The fission of the primary cell underlies the identical quantum-biological factors as the processes in the development of the primitive phases. The FILUM is suddenly projected in the identical way. In the small space of the spherical primary cell, it is confronted with a considerable space problem so that only a very short thread results (the FILLELUM). The new symprotit is formed by the tiny button growing at its end. It swells up to the same size as the mothermych.

With this, the spherical bacterial cell begins to stretch and it gradually ties itself up in the middle, whereby the FILLELUM gets absorbed. Subsequently, the fission of the tied-up two-nucleic cell into two bacterial

spheres with one nucleus, each, occurs. An additional construction phase of two mychits into a short rod is the bacterial form of double rods, then fourfold-rods, then eightfold rods, the six teenfold-rods and then thirtytwofold-rods. The final product of this developmental sequence is the BACTERIAL TUBE, the ASCIT. In all these developmental forms, the mych (primary nuclei) lie one behind the other (catact), while they are usually arranged in an irregular way towards the sides (synascits) in more progressed forms.

The primary nuclei (mych) of the bacteria remain in the majority of the bacteria placed at the wall, the mych usually protrudes only minimally from the bacterial contour, rarely noticeably far. Only in the synascits, which are the very thick bacterial forms in which the primary nuclei (mych) are present also in the interior, and even more, in the mycelia of fungi, they are not placed at the wall.

Reserve substances, which form a more or less thick layer, may be deposited around the primary nucleus. These mych with their covering of reserve substances completely correspond physiologically to the fatty substances in higher organisms. To the very largest percentage of cases, these reserve materials consist of LIPOIDS and also of NUCLEIC ACID DERIVATIVES. Both of them have a strong capacity for taking on coloring agents, in contrast to the extremely low capacity of the bacterial nucleus to be colored (stained).

The mych (nucleus) is only visible in the spherical bacterium (mychit) when it occurs without reserve materials (atrophic), which usually happens only in strongly parasitic varieties, as with for example CHOLERA BACILLI or MEMINGOCOCCI, which require no nutritional reserves.

#### THE PRIMARY NUCLEUS AND ITS FISSIONDUM-BELL SHAPE IS, RATHER, THE PRIMITIVE FORM OF THE CHROMOSOMES.

Among the growth forms of bacteria belong also the partial formations, which get tied off at the end of a bacterial thread; they may also be spherical propagation forms, that is mychit which are named GONIDIA in this function, or also parts of double-rods or fourfold rods for reproductive and spreading purposes. The permanent spores (SPORITS) also belong into this group, in which a portion of the nucleic protein gets stored in dry form. These dry forms of sporits can tolerate temperatures up to 310 degrees celsius (according to Prof. Zettnow, Robert Koch Institute), or higher yet (according to Dr. Spengler), without their germinating capacity being damaged. While there is a sharply-comparative morphologic cut between the primitive phases and the bacterial phases, there is no such occurrence between synascits of bacteria and synascits of fungi; they smoothly merge into one another.

The spore formation of fungi is of a manifold nature. One portion is a combination of an inner germ out of the spore, in the form of a fungal thread which GERMINATES IN NEUTRAL AND ACIDIC MILIEU, and also of primitive phases distributed over the surface, which germinate in ALKALINE MILIEU. This signifies nothing other than a securing of progeny under all possible conditions of nature.

#### THE DEVELOPMENTAL PROCESSES IN THE BLOOD

Our blood preparations show the just described formations and reformations in abundance. When we take a closer look at the individual sections of the slides in the diverse microscopes, and compare their forms with one another, it should become quite clear to us that there is a constant microbiological process taking place in our body fluids, the action of which must be immensely important for the condition of the human being.

Now we are facing the developmental processes in these microbes which are so decisive for the human health. They may occur singly, or also in manifold ways.

1. THE MULTIPLYING DEVELOPMENT (AUXANOGENY)
2. THE CONSTRUCTIVE DEVELOPMENT (PROBAENOGENY)
3. THE NUCLEIC CONSTRUCTION (DYNAMOGENY)
4. THE TENDENCY FOR CHANGING QUALITY (PHYSIOGENY)
5. BLOCKING (MOCHLOSSIS) AND UNBLOCKING (MOCHLOLYSIS)
6. THE SEXUAL PROPAGATION
1. THE MULTIPLYING DEVELOPMENT (AUXANOGENY)

The multiplying development represents that development, which is commonly known and recognized. A bacterial sphere (mychit), a short rod (dymichit), or a long rod grows to its double size and then splits in to two individuals of half the size. This process of development, however, is possible only WHEN THE CULTURE IS SUPPLIED WITH AN EVER NEW NUTRITIVE MEDIUM. This is also the reason for the very old demand in microbiology to work only with entirely fresh cultures.

## 2. THE CONSTRUCTIVE DEVELOPMENT (PROBAENOGENY)

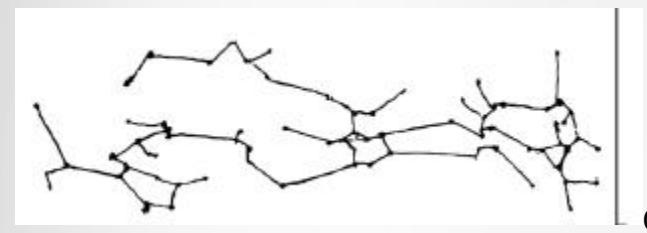
It is based on the quantum-biological sudden leaps. Each microorganism forms from within itself ferments in each of its developmental phases, namely the SPECIFIC ORGANIC ACIDS, which prepare for this advancing development. The dependency of probaenogeny upon the pH of the nutritive medium or the milieu is a FUNDAMENTAL LAW (Enderlein calls it ?Anartatic Fundamental Law?). The changes of the hydrogen-ion-concentration, from the strongly alkaline high of the pH-value towards the ever decreasing pH-value of the acid side, constitute the

fundamentals of this law for giving the ever higher advancing microorganism the capacity for use of all its lower developmental forms to serve its advancement into ever newly developing organic form. That is, it demonstrates the summary of the ASCENDING developmental tendency with the ever more DESCENDING pH-value. The fact that this is due to internal valences, is proven in that ONE CAN NEVER FORCE AN ADVANCEMENT through increasing the acidity of the culture medium, even by supplying that specific acid which has been found out to be the one formed by the organism itself for this advance. In contrast, a DESCENDING DEVELOPMENTAL TENDENCY to the lowest forms of the total cycle can be reached extremely easily. By adding a little bacterial material or parts of fungal mycelia to a hanging drop of 5 % sodium carbonate, that is, a strongly alkaline medium with a high pH-value, one can immediately observe the formation of the primitive stages, namely in the CHONDRT STAGE. That is, one can easily verify the advancing steps ?PRIMITIVE PHASE - BACTERIA - FUNGI?. For this, it is all the same whether one uses mycelia from a mould fungus or from a yellow boletus in the forest.

THUS, IT IS A BIOLOGICAL REALITY, YES A TRUISM, THAT, WHEN LOWER BACTERIA DEFICIENT IN ALKALINITY, AND FUNGAL FORMS OF EVERY TYPE (such as mould fungi) WITH A DEFICIENCY IN ACIDITY, ARE BROUGHT TOGETHER ON AN AGAR PLATE, THEY RETARD EACH OTHER?S DEVELOPMENT AND BECOME MUTUALLY EXCLUSIVE.

Now to continue with the developmental stages. All microorganisms have two forms of growth which continuously alternate. The primary stage, the PROTIT, represents the ongoing changes between the primary granule (PROTIT) and the double -granule (DIPROTIT). Thereupon follows the primitive stage FILIT, the ongoing change between the FILUM and a filum-piece of double its length. For instance, the

FILIT occurs in the genesis of the fibrin. Enderlein counts this in with the cycle of the endobiont.



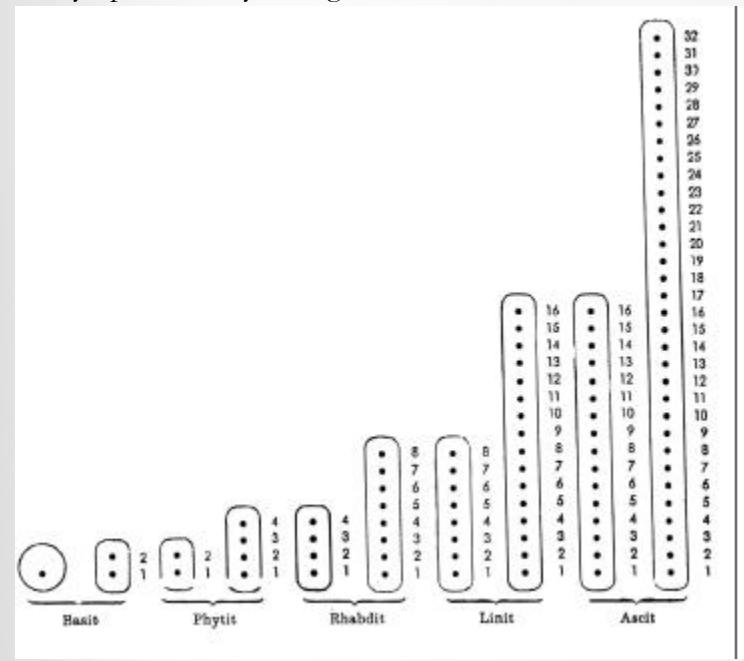
Endobiont

chondrit-stage in blood serum Enlargement 10 000 : 1.



Endobiont

Chondrit-stage in blood serum. Erythrocyte on which the chondrit flake is based, since many symprotits, very strong & mobile.



Leptotrichia buccalis (Robin 1879), Enlargement 20 000 : 1.

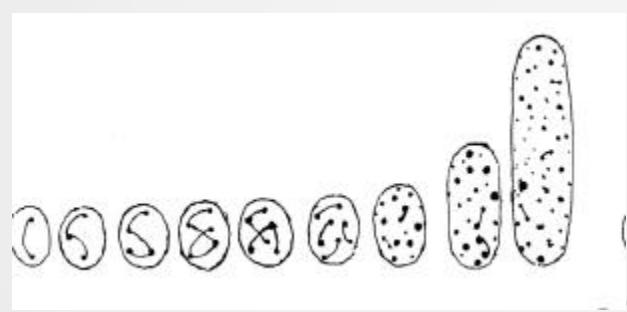


Bacterium broteus Hauser:

Fig. 1 = basit stage, fig. 2 = phytit stage, fig. 3 = rhabdit stage, fig. 4 = limit stage, fig. 5 = catact ascit stage, fig. 6 = synascit stage (terminating into ascit on the top).

The primitive stage CHONDRIT can be seen most frequently, the constant change between FILUM and PRIMITIVE GRANULE (Symprotit). Depending upon the size of this tiny primitive granule (between 0.02 pm and 1 pm), very diverse valences may occur at this stage, all of which can present diversified needs and properties.

The BASIT-stage consists of an ongoing change between individual sphere and a very short twofoldrod. Among these are the cocci forms of bacteria, which already present primary cells. Subsequently, the stages conclude with PHYTIT, RHABDIT, LINIT, ASCIT AND MICASCIT, depending on the change between twofold, fourfold, eightfold, sixteenfold, thirtytwofold or longer rods. Because of their manifoldness, all these stages are collectively named SYNASCIT, which is their collective-stage name.



Leptotrichia buccalis (Robin 1879), formation of syntact ascits (= synascits), Enlargement 20 000 :1.



Sclerotrix tuberculosis Koch 1882, Mychomitosis inside Mychit. Nonacid-fast form, Enlargement 10 000 : 1



Sclerotrix tuberculosis Koch 1882, copulation of 2 mychits in basit-stage, nonacid-fast form, enlargement 10 000 : 1

The PATHOGENITY of each microbial parasite lies nearly always in ONE developmental stage, the VIRUS STAGE, rarely in two or even more stages. This VIRUS STAGE may occur at any place within the total developmental course. ONLY IN THE PRIMARY PARASITES OF HUMAN BEINGS, WHICH ARE CONSTANTLY PRESENT IN THE HUMAN BODY - THAT IS, THEY ARE NOT ABSENT AT ANY POINT OF THE TOTAL HUMAN DEVELOPMENT - IS THE TOTALITY OF THE MANY HUNDREDS OF DEVELOPMENTAL PHASES MORE OR LESS PATHOGENIC. This pathogenicity rises with the level of the developmental stages and their dynamovalences.

THE ONLY EXCEPTIONS ARE THE VERY FIRST PRIMITIVE STAGES, named the PROTIT and the CHONDRITS which are of lowest valences. They are entirely nonvirulent and they play a REGULATORY role toward the higher and pathogenic stages by decomposing these through copulatory processes. In that sense, these stages are termed REGULATORS.

Let it be added, that beside each of these numerous developmental possibilities, also additional stages may simultaneously occur, especially all low stages. EACH OF THESE STAGES IS CAPABLE OF PRODUCING THE CHONDRIT-STAGE OUT OF ITSELF. But, the microorganism is also capable of presenting the higher stages by leaps, in conformity with the quantum-biological and atom-physical nature of the primitive processes of these lowest of living organisms.

3. THE NUCLEIC CONSTRUCTION (DYNAMOGENY) If the microorganism finds no possibility and no preconditions for reaching a higher stage, then it accumulates its living energies in one or more, or even all of its nuclei (mych) so that, when other living conditions prevail, it will be immediately in the position to leap suddenly into the construction of a complex organism for which it already has the necessary materials. This behavior lends to the microorganism a certain independence from the other developmental processes.

4. THE TENDENCY TO CHANGE THE QUALITY (PHYSIOGENY)

It also needs not always run parallel to the other developmental processes. For example, consider the change between acidproof and non-acidproof qualities of the tubercle bacillus.

5. BLOCKING (MOCHLOSIS) AND UNBLOCKING (MOCHLOLYSIS)

This concept also is very important.

Examples: In higher organisms, the changes between the individual developmental stages are connected with more or less penetratingly big differences in the necessities for life. A variety of the bark-beetle, living in a decomposing tree, has identical necessities for life of the egg, the four larval stages, the pupa and the bug himself. This is entirely different for a mosquito: the egg, the larva and the pupa live in water, the mosquito in the air, and it is blood-sucking. These identical differences occur in the microorganisms in very much manifold numbers. There are bacteria, such as e.g. the diphtheria bacillus which occurs both in the pure culture and also on the tonsil, simultaneously as spheres, short rods, long rods, club rods, cystit, thecit, yes, even in yeast form.

All these developmental stages have, therefore, the identical necessities of life; they are ISOBIOTIC. However, most bacteria are biologically oriented in a HETEROBIOTIC way, that is, the individual, cyclic, developmental stages may have diverse necessities. Their rise or descent will break down when these necessities find no satisfaction. This very frequently insurmountable appearing blocking (MOCHLOSIS), hindering the further development, has been one of the most important foundations for a monomorphism.

A MOCHOLYSIS (or UNBLOCKING), that is the resolution of obstructions, can be reached through the effect of influences which favorably change the pH of the culture medium. Another aspect are the internal influences of the bacteria itself, namely the FERMENTS. We are here also partly dealing with spontaneous, quantumbiological changes. These factors are e.g. light, electricity, removal of oxygen, presence of special gases, toxins, salts in various concentrations, parasitism, chemicals, thermic changes, etc.

Particularly for our endobiont, the main factors which threaten our health are: cancerogenic substances, purely mechanical stresses, the lifestyle and the diet, which are CONDITIONAL factors for its rising development. The CAUSATIVE FACTOR IS THE ENDOBIONT HIMSELF. Together, these are the factors which bring about the consequences, namely, that the human being - as the host of this primary enemy - is attacked in increasing degree by rheumatism, circulatory disturbances, dropsy, stroke, diabetes, stomach ulcers, and finally also cancer.

Enderlein calls the summit of the microbial development THE CULMINATION. If the CULMINATION lies in the BASIT STAGE, then there are involved the species of micrococci, streptococci, diplococci, etc. If it lies in the CHONDRIT STAGE, then the microbe is the cause of a so-called VIRAL disease. Most of the CULMINATIONS exist in the fungal form, especially in the mould fungus forms as well as in the yeasts can present the CULMINATION, such as e.g. in diphtheria. For our primary enemy, the culmination is the fungus MUCOR RACEMOSUS FRESEN, with its bacterial phase LEPTOTRICHIA BUCCALIS (Robin 1879) (according to modern classification = PROPIONIBACTERIUM ACNES), which can always be found between the teeth and on the gums of human beings.

## 6. THE SEXUAL PROPAGATION

The sperms of the microbes are tiny swimmers that consist of a tiny symprotit head and a filum flagella, which enables it to copulate with all symprotits or mych of all the bacterial and fungal forms within the

same cycle. The consequence of such propagation of bacterial and fungal-nucleic apparatus (mych) is naturally that the bacteria and fungi immediately become dissolved and they degrade. However, this is on no account identical to the damaging or destruction of the bacteria, as the bacterial researchers had assumed. They had believed that the bacteria were simply eaten up. Rather, we are dealing with THE TRANSFORMATION OF PATHOGENIC BACTERIA INTO THEIR NONPATHOGENIC PRIMITIVE PHASES WHICH, BEING UNINTERESTED IN A PARASITARY LIFESTYLE,

IMMEDIATELY LEAVE THE HUMAN BODY. This elimination of the primary enemies in a peaceful, living manner from the body occurs by way of the epithelia, the bladder, the intestines, and the bronchies.

## PRACTICAL EXAMPLES

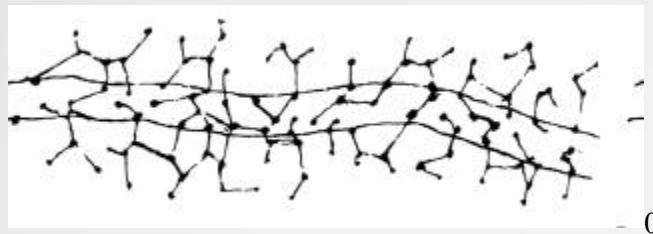
If one observes the comparative-morphologic blood condition of a patient who has the FELTY syndrome (a special form of PCP with tumor of the spleen, leucopenia, anemia, and brownish pigmentation on uncovered body surfaces) - even if he still walks about in apparent health, one is amazed and fascinated over the manifoldness of the biological occurrences in his blood. One can see how numerous erythrocytes helpfully approach leucocytes and lymphocytes that are seriously attacked by symprotits of the endobiont; they crowd around diseased white blood cells.

THIS DRIVE TOWARDS PROXIMITY IN ALL CYCLIC DEVELOPMENTAL FORMS OF BACTERIA IS CALLED ?SYMPLASTISM?.

One can observe how the parasitic symprotits are transferred onto the erythrocytes and how they fill them very densely. Additionally one can observe how, in those erythrocytes that have removed themselves from this place of stress, the symprotits enlarge more and more, assuming the cellular form of thecits and frequently having three to six primary nuclei (mych) then being moved to the surface by the erythrocyte and expelled from the lumen. When we observe these exiting thecits precisely, we note with amazement: they resemble the thrombocytes, like one egg looks like the other, and they blend into the blood situation fully in this role. Frequently, they are expelled in the form of chains, but also in distinct forms of rods that belong to the bacterial form of the endobiont, namely, the LEPTOTRICHIA BUCCALIS.

It is especially remarkable that the leucocytes and lymphocytes also digest all bacteria and cocci, after eating them. But the endobiont has succeeded through vast realms of time (since its primary impact) in overcoming this digestibility and - although the effectiveness of destruction of the parasites is there - however no longer for the endobiont. These indigestible organisms are passed on to the erythrocytes, which take them over, expelling the parasite in the form of a thecit, and thus they return into the bloodserum in the form of thrombocytes. Thus leucocytes and lymphocytes can be freed of the parasites. This process is often observable with the Felty-syndrome. However, in cancer cases this detoxifying action occurs very rarely with such force, so that the erythrocytes do not succeed in liberating the leucocytes or lymphocytes from the parasites.

If we, however, observe the identical course in the blood of a cancer patient and a Hodgkin patient, one can likely detect in them quite similar processes. Only, in these cases, the leucocytes and lymphocytes are so massively invaded by parasitary symprotits that the help and force of the onrushing erythrocytes cannot match them. They are so massively stuffed full, and the symprotits enlarge themselves in the erythrocytes to very thick, nearly dry protein ?SPOROID SYMPROTITS?, so that a further development of the symprotit into thrombocytes within the erythrocyte is entirely impossible. Also, in cancer patients, through the diminished defensive capacity of the erythrocytes, there is nearly always no expulsion in the form of thrombocytes. The catastrophic condition of the leucocytes and lymphocytes corresponds with this, in that their plasma is in most cases fully or nearly completely degraded. In such blood, there are frequently only nuclei of these white blood cells remaining, which moreover host masses of parasites. They frequently enough fall apart themselves into symprotits of the parasite, which often immediately develop themselves further into thrombocytes. This further debilitates the lowered defensive capacity and absorptive capacity of the erythrocytes.

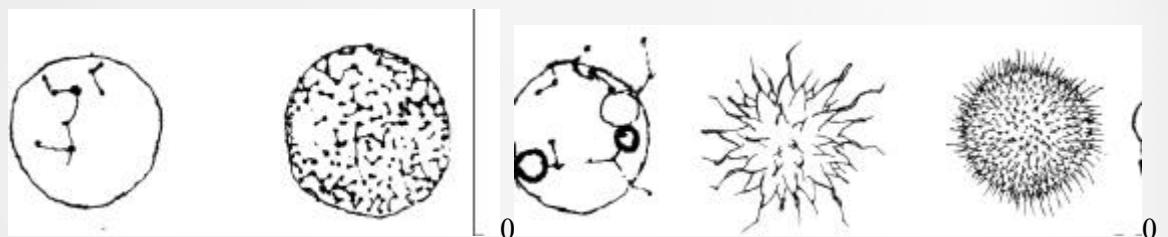


Many chondrit-dendroids within and outside a nervefibril in rheumatism (tree-like), Enlargement

3000 :1.

#### SOME COMMENTS FOR MEMORY AID FOR THE BLOOD EXAMINATION

The CHONDRT FORMS swarm *very* often freely around in any blood as ?swarmers ?, consisting of a symprotit head and a filum flagella. If they are found swimming freely in the blood serum, arranged in tiny trees, then we are dealing with a beginning endobiotic disease, especially rheumatism. However, the seriousness of the illness is visible from the valence, that is from the relative size of the symprotits. The significance of the dynamovalence of the symprotits can be seen from the following illustrations.



Erythrocytes with different valences:

From patient with metabolic disturbances and swelling of the liver.

From patient with cancer.

Erythrocyte from Erythrocyte with cancer case (Berlin especially low April 1952) live blood valence picture. Especially endobiont high valence end- infestation. dobiont infestation.

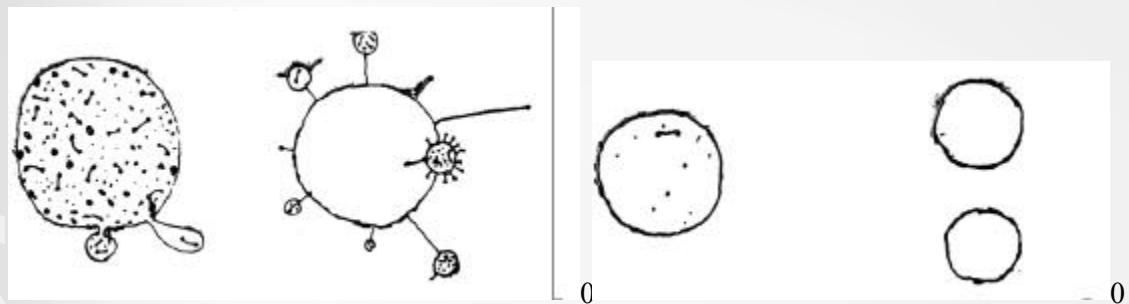
From the marginally situated symprotits on the erythrocytes - also - bacterial rods may form when there are higher dynamovalences, among which is cancer. The possibility for building other forms of the developmental cycle is, generally speaking, actually entirely unlimited.

The causes for stroke lie in the area of congestive processes in the developmental stages of the congestive agent (endobiont). Another possibility is the ?SYMPLASTISM?, the drive toward symplast formation, which is inherent in all developmental phases of the bacteria within a certain physiological condition which, undoubtedly, arises from a tendency to

wards a stronger alkalinity. In this symplast, all developmental forms get densely packed together and degrade in a massive copulation of the MYCH amongst each other, and they frequently end in a total

agglutination of chondrits and protits.

An additional, fundamentally significant factor is the process of erythrocytic parasitism and the further development of the endobiont in this element of blood !!!



Erythrocyte with Enlarged isolated symprotits + thecits thecit. situated at the end of

2 Colloid-thects very strongly light refracting (like glass the respective filum. lense).

When we observe the blood of a patient with anemia, we note that the endobiont can develop itself further in the forms of: symprotits and their splitting dumb-bells, thecits, thrombocytes and bacterial rods, with more or fewer primary nuclei, depending on the formation of their size.

A very important point must be taken into account. The copulation processes in the chondrits brought into the human body are, in no case, singular occurrences. Rather, they continue to copulate ongoingly. That means, when congestions occur involving these degradation products and their deficient elimination, these metabolic products also copulate again and again, also amongst each other.

Therefore, if these metabolic products are not properly eliminated from the body, the valence of pathogenicity continues to rise the longer this ongoing copulation continues. From this, it must be decisively seen that no lengthy pause may be allowed between a chondrit injection (e.g. MUROKHEL) and the anti-chondritin injection (e.g. MUROKHEL EXCRETION PRODUCT) except in cases with free ways of elimination of all degradation products. A correct combination of all these possibilities is, therefore, the basis for success for a good doctor.

Of special importance is the comment that the so-called dysbacteria of the intestines in cancer, Hodgkin and other diseases from the endobiont complex are in no way degenerative coli-bacteria, as is often stated, but those degradation products of the endobiont in their chondrit-stage which are moving along through the intestines are reconstructing themselves into the short rods of the Leptotrichia buccalis. Because this repeated infestation by highly pathogenic forms causes serious intestinal disturbances, especially obstipation, which represents a serious stress during the cancerous process - it is urgently advised to take care, AND immediately to take orally - best time, in the evening - one endobiont-chondritin-tablet (MUROKHEL D5), or better a capsule (MUROKHEL D4), which will cause a repeated degradation within a short time. Only after freeing the intestines from such dysbacteria would it make any sense at all to ingest again a full-value coli-bacterial strain in place of the one ruined through the dysbacteria in the

intestines.

#### FURTHER COMMENTS

##### THE EFFECTS OF THE MICROBIOLOGICAL PROCESSES IN THE BLOOD

First of all, importance must be placed on the level of the developmental stage of the parasite. It is increasingly recognized that certain disease types are not produced just by one and the same parasite, but much more frequently by a whole series of agents, but in a very definite developmental stage of the causative factor. IN SUCH CASES, THEREFORE, THE DEVELOPMENTAL STAGE OF THE PATHOGENIC PARASITES IS THE DETERMINATING FACTOR!!! For instance, it has become known that rheumatism is caused by the chondrit stage of several different organisms, thus, normally, the endobiontic rheumatism by the endobiont; but also by the tubercle bacillus in its chondrit stage, the so-called Poncet's rheumatism; then, additionally, also the chondrit stage of the lues pathogen, of the gonococcus and a whole series of streptococci and micrococci. THAT IS TO SAY, THE STAGE OF THE PARASITE IS THE DECISIVE FACTOR.

The blood of every human being also contains in the condition of total health numerous elements of the developmental cycle of the endobiont; this constant infestation exists partly free in the serum, to a large part in the erythrocytes, and especially in the lymphocytes. Add to these the fibrin and, especially, the thrombocytes, the blood platelets, both of which have proven themselves to be elements of the cycle of this parasite.

Parallel to the disease symptoms, different forms in the cyclic process of the endobiont go through all three chief phases, which are present in all tissues and organs. Every single one of the multitude of endobiosis diseases is chronic, general illness of the entire human body. Among all these tissues, blood tissue is the most accessible to a critical examination.

The endobiont is a pronounced ROBBER OF PROTEIN. The only non-plant protein which can be taken in larger amounts, is the protein of the milk, and that in its acid form, such as cottage cheese and other forms of cheese. These lactic proteins have developed a special accomplishment in the course of endless time, namely the capacity for producing a specific protein synthesis, which does not give the endobiont an opportunity to feed on.

#### BIPOLARITY OF THE CHRONIC DISEASES

The one side of this bipolar construction acts alone through the FAULTY OPERATION of all physiologic processes and factors. This is the aggressive method of the tuberculosis-bacillus and of the paratuberculosis agent in its primitive stages. The other side is represented by the CONGESTIVE METHOD of the endobiont. The endobiont has a congestive influence simply by its presence in every case, and this, in three diverse ways, namely, to begin with, by its primitive phases, later through its bacterial phases, and finally through its fungal phases. Thus, parallel to the rise in valences and the developmental phases, this also raises the pathogenicity, simply by increase in its mere size.

#### METHOD OF THE BLOOD EXAMINATIONS

The many appearances of the chronic disease complex are due to the unlimited hundreds of developmental phases of their microbial agents. Not only do they attack all tissues and each individual cell, but they also express their extensive, primary appearance in every fully healthy human being, even in all body fluids of the entire organism.

While the developmental form represents the ONTOGENY in all plants and animals, the organizational capacities within the primary organisms have potentized themselves into a fourfold possibility:

1. CYCLOGENY It represents a limitless potentized summary of a huge number of generation cycles in which each single appearance-form is ABLE TO REPRODUCE ITSELF INTO THE IDENTICAL FORM AS LONG AS AN IDENTICAL pH IS MAINTAINED. The colloids, being the primary construction material, form primitive nationalizations through lining up these primary factors, namely:

- a) one-dimensional, that is, arranged in threads (filum)
- b) two-dimensional, into finest, skin-like surfaces, which are found e.g. in the spermit (bacteriophage) as swarmer-heads
- c) three-dimensional, namely into physiologic, often spherical symprotits (primary nuclei)

Both the filum and the symprotit alone are already able to unite themselves, namely, the first into the FILIT, a constant change of fila sizes  $x:2x$ , the latter into the stage SYMPROTIT, a constant change of symprotits in spatial sizes of  $x:2x$ .

For all remaining developmental phases, only these quoted building blocks are used for the higher and highest nationalizations. That is, they are not only used for the construction of the bacterial phases but for all phases of the fungal forms.

2. ONTOGENY This means, the developmental form of all plants and animals which, however, here in the primary organisms, depends on the ANARTATIC PRINCIPLE (Enderlein). This means: for the nationalization of comparative-morphologic units into higher and highest developmental phases, the specific acids PRODUCED by each individual microorganism are the CAUSAL reason for the changes of the milieu in the pH, and that is tending to the ACIDIC side. In other words: the RISING steps of the total cyclogeny are accompanied by and dependent on the PROPORTINATELY DESCENDING pH. (This has been incorrectly assessed as ?pollution? by bacteriologists.)

#### 3. SYMPLAST

This is not a stage but an extremely diversified form of conglomeration. Developmental forms of every type within the total cycle have the tendency of agglutinating into more or less formless spheres (SYMPLASTISM). In this process, all individual phases fall apart into the primitive phase CHONDRIT, the constant change between filum and symprotit. Thus, THE SYMPLAST IS AN EXTREMELY PRIMITIVE FORM OF THE MERGING OF ALL FORMS FOR INCREASED SEXUAL COPULATION.

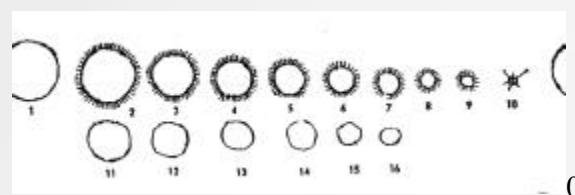
#### 4. SYSTATOGENY

When they occur in concentrated form, the last units of living substance (the colloids, directly connecting with the atoms, are capable of structuring themselves through an inherent drive towards arrangement. Even through minor impacts are they driven into the so-called SCAREFORMS, which represent forms of dry protein, looking like crystals and being highly reflective. In this form, they survive temperatures of over 310 degrees celsius without loss of germinating capacity. These pseudo-crystals are often found in the blood of chronically ill patients. They need not necessarily come from the same provenance because colloids of different species can unite with one another. They mostly stem from the endobiont, of which we know from experience that it feels obliged in all cases of infectious diseases and epidemics to spread itself especially broadly so as to intensify the pathogenicity of the infectious disease into its worst form.

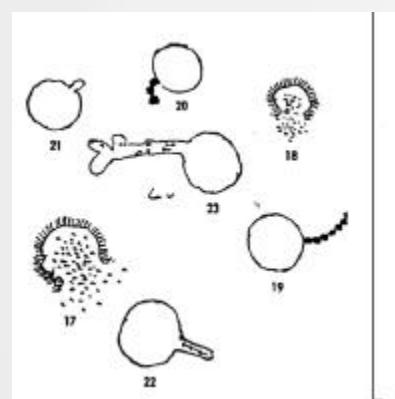
## FORM FOR BLOOD EXAMINATIONS

### 1. PROTIT VEIL

The presence of a veil drawn over the entire visual field indicates the tendency to freely release the final units (colloids) in masses and, correspondingly, a very high alkalinity, a very high pH. When the native preparation shows this condition, then it is useless to supply injections into such a phase because they must remain ineffective. No formation of spermits will occur in this condition, and already present spermits get immediately degraded into colloids through the injection material. Therefore, all too strongly alkaline blood-conditions must be optimally adjusted toward the normal degree for the spermit. For this reason, a preceding application of FORMIC ACID D6 (D5/D4) or L(+)-lactic acid potency accord (SANUVIS), BEFORE the chondritin injection, has been practiced for years. THE OPTIMUM PH FOR THE SPERMIT IS ON THE LEVEL OF 7.3.



Blood elements: Collection directly after blood-vital examination fig. 1 erythrocyte, fig. 2-9 8 examples of dioekothecit of the size of ery? s til the size of a thrombocyte; with thick & hairlike fila which are extraordinarily short and equal and extend longitudinally. fig. 10 A thrombocyte for comparison. fig. 11-16 6 colloid-theccits from the same blood in different sizes.



A few blood-elements, approximately 4 hours after blood was obtained, fig. 17 and 18 degrading dioekothecits. fig. 19 and 20 erythrocytes with 1 chondrit thread each with larger symprotits and very short fila parts. fig. 21 and 22 two erythrocytes with catatact ascits. fig. 23 erythrocyte with synascite vital.

### 2. COLLOID THECIT + DIOEKOTHECIT

a) COLLOID-THECIT: A developmental phase of the primary parasite. It is spherical and may show any size up to the size of erythrocytes. It consists of

a heap of pure colloids arranged as a sphere, which is surrounded by an extremely fine spherical shell, and shows no sort of appendices, such as even the shortest form of fila. Only in the darkfield alone is it even noticeable. Even this takes great practice in working with microscopes. In cases of cancer and other serious endobiotic diseases, the tiniest and up to larger conglomerates of colloidal masses occur as shadowy, extremely delicate, grey spheres or spherical formations. They do not contain traces of one or more nuclei, thus representing ?cells without any type of nucleus. ? In the darkfield they show a weak glimmering. Normal chondrit- theccits with abundant primary nuclei begin with minimal nuclei, which occasionally can fill up the theccits rather densely. The final function of the colloid-theccit is the formation of large numbers of free colloids through tearing of the extremely delicate covering membrane.

b) The DIOEKOTHECIT is similar. It is filled with the absolute tiniest primary nuclei, the ?micromych. ? That enables it to release conspicuously densely protruding, very short and fine fila through its extremely thin spherical enveloping membrane. Their size lies between the size of a thrombocyte up to the size of an erythrocyte. We are dealing here with nothing other than a gigantic thrombocyte, which does not contain the typical 3-7 mych but many hundreds of such mych. The final function of the DIOEKOTHECITS is the formation of spermits, through the tearing of the extremely delicate enveloping membrane. Both these formations are indicators of defensive capabilities. This DIOEKOTHECIT is not seldom found in the blood, but generally only in +/-small numbers. The genesis of these parasitic blood-elements of the endobiont stems from the erythrocytes, that is, these giant thrombocyte-type developmental forms from the cycle of the primary parasite are expelled out of the erythrocyte. Accordingly, the erythrocytes have a lumpy, pseudocrystalline appearance because they have been damaged very much through the attack of the primary parasite.

### 3. FILIT PHASE

It can be observed only in the darkfield. It is the first of the primitive phases which occurs through the change in fila according to the formula  $x:2x$ . Because the x shows very great differences in the lengths, the filit-phase comprises very large numbers of individual phases.

### 4. SYMPROTIT PHASE

One can tell by the diverse sizes of ?free symprotits which are present, whether one is dealing with a pure developmental stage. Namely, in that case, the formula is also  $x:2x$ , which means the presence of identical spheres plus other ones of twice their size. When several sphere-phases are found side-by-side, they will be indicated by a larger number of varieties in size, which is the more common condition.

### 5. MACROSYMPROTITS

These represent exceptionally large spheres of purely nucleic protein. They can be found free, or connected with the filum, or in the elements of tissues and cells of the host. In connection with the filum, the fila are, then, usually very mobile.

### 6. SPOROID SYMPROTITS

In the viewfield of the microscope, these appear as smaller or larger, luminous spheres, representing symprotits that contain protein substance in dry condition. Also, these already have all properties of the sclerotic developmental forms of the parasite and can survive heat of 310 degree C. They may occur either in the erythrocytes, the leucocytes, or simply by themselves (free).

### 7. SPERMITS

This phase develops out of the filum by growing of a symprotit-head on one of the two endings of the filum. We are here dealing with the integration of two different developmental phases, in which the filum takes on a flagella function. The presence of spermits in the blood-sample is always a sign for defensive capabilities against the higher, pathogenic phases of the endobiont. The spermit is nothing but a readiness to meet an alarming situation.

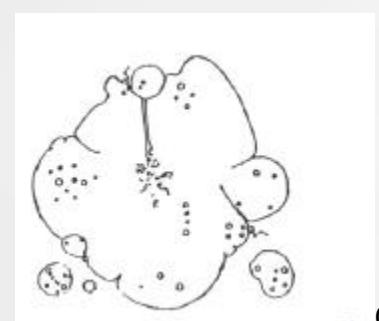
(Illustration not possible because of the minute size and mobility!)

#### 8. FREE CHONDRITS

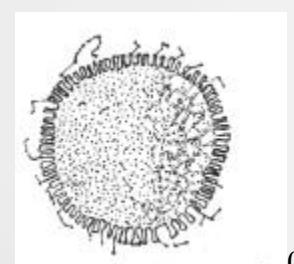
The chondrit stage begins with that sphere of the developmental growth of the endobiont, in which only the low-valenced phases have full apathogenicity and all higher phases reach pathogenicity to an ever rising degree. Not only the enlargement of the symprotits (that means, their valence) of the fila causes the rising lively mobility of fila but also the denser arrangement of even tiny symprotits along the length of the fila.

#### 9. COLLOID SYMPLASTS

These are conglomerations of colloidAecits (cells without a nucleus). Only in the ongoing course of these conglomerations do the symprotits, and also especially the sporoid symprotits arise within these symplasts. They are a strong hindrance factor in proper blood circulation.



3 colloid symplasts with sporoid symprotits and beginning formation of chondrits inwards and outwards. Added an erythrocyte. Patient = sarcoma upper jaw.



Large round vesicle, apparently formed out of agglomerations of thrombocyte. Within the spherical envelope short bacterial rods are tightly packed together.

Worm-like, big colloid-symplast with numerous bundles of the filitstage (6 erys for comparison).

Big edging colloid-thecit with filit bundles and 7 golden, glaring, sclerotic pseudocrystals (which can be

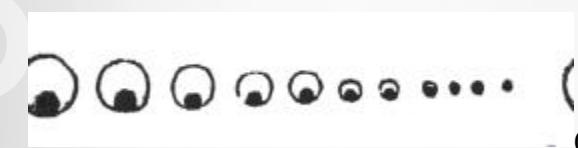
silver-white).

#### 10. MYCHITS (bacterial spheres)

The presence of reserve substances around the bacterial nucleus is of great importance for the mychits. To the most part, they consist of lipoids and nucleic acid derivatives. According to the absence or presence of these nutrients, the mychits can be classified: a) atrophic, b) miotrophic, and c) pliotrophic cells.



Bacterial forms of the endobionts. Development of a mychit (primary cell) out of symprotit, the latter develops into a mych (primary nucleus).



Sclerotrix tuberculosis Koch 1882, primary cells (mychits) and transitions into free symprotit, nonacid-fast form, enlargement 10 000 :1.

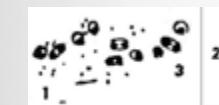


Fig. A Mychits (2) dimychits (3) as well as tiny simprotits (1)

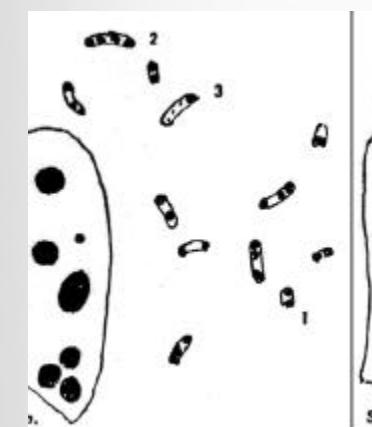
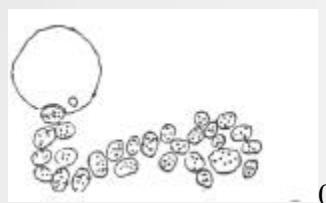


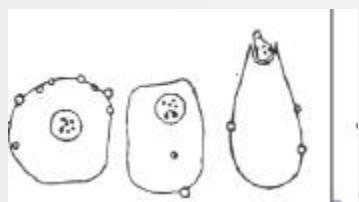
Fig. B Some bacterial forms with four dimychits (1), 8 didimychits (2+3) Sa. = synascit with 6 trphosoms and 1 trophosomellum.

11. THROMBOCYTES, MICROTHROMBOCYTES All thrombocytes entirely belong into the cycle of the primary parasite (endobiont) of the human being. They arrange themselves freely into the extremely manifold areas of the THECITS. In lymphatic leukemia, Hodgkin, etc. the tendency may arise for all parasitic elements to degrade into the tiniest cells with uncommonly tiny nuclei, so that all cells, and parti-

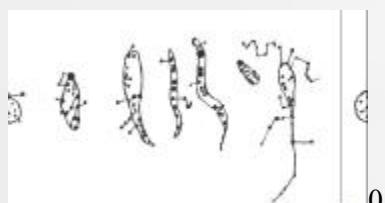
cularly the leucocytes, get densely stuffed full with the tiniest microthrombocytes. The essential factor in thrombocytes and microthrombocytes is THE NUMBER OF NUCLEI which is between THREE AND EIGHT primary nuclei. All the larger ones are better classified among the thecits or - if they reach bacterial form, which is frequently the case - among the catabact ascits and the synascits.



Erythrocyte with serial ejection of thrombocytes. One sporoid symprotit remaining in the erythrocyte. (Hodgkin patient).



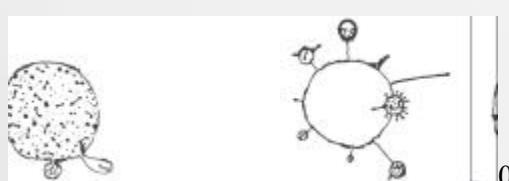
Three thrombocytes in process of leaving an erythrocyte each. Patient with anemia.



Seven different thrombocytes, only the first of which is normal. ,

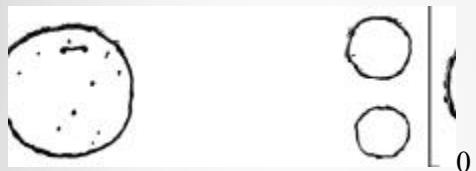
## 12. THECITS

This very frequently occurring developmental form represents the primitive, primary form of all bacteria in the original sphere-shape, having more or less primary nuclei. The mych (nuclei) may be developed in the very tiniest form, up to extraordinarily large nuclei. From this form, all bacterial rods have emerged phylogenetically through differentiation.



Erythrocyte, completely degraded, with 2 pedicle free exited thecits.

Erythrocyte with symprotits and thecit at the end of a filum each.



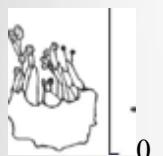
Isolated enlarged thecit.

Patient with anemia

Colloid thecit, very strongly light-refractory like a glass tense.



Erythrocyte with exiting fila, at their ends symprotits or more or less enlarged cystits.



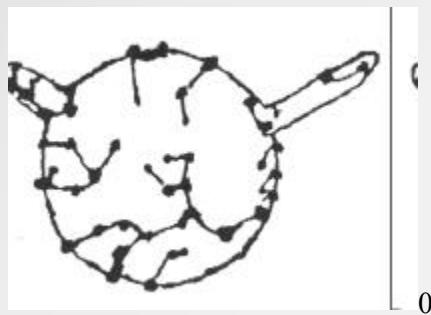
Erythrocyte with end symprotits which have already developed into thecits in the form of thrombocytes.

## 13. BACTERIAL RODS + ASCITS

The presence of bacterial forms with catabact arrangement of primary nuclei in the blood-samples IS ALWAYS A SUSPICIOUS SIGN. If they occur more frequently, ALONGSIDE OF OTHER SIGNS, then they are a sure documentation for either the presence of cancer, harmless or malignant tumors, or a serious chronic disease. They usually develop in the blood from the so-called ?marginal corpuscles? (symprotits) of erythrocytes. Reaching a certain length, they free themselves, whereby they flexibly search around with their front ends (like ?tiny worms?). The diverse lengths of these rods indicate their association with particular developmental stages (phytit, rhabdit, linit, ascit). (Figures and photos after no. 14)

## 14. SYNASCITS

The formation of syntact rods (with their nuclei arranged in all directions is a sign of further, rising development and therefore also documents rising pathogenicity.



Erythrocyte from a patient with stomachcha. With 2 exuding bacterial rods of the endobiont. Enlargement: 3000 : 1.

Leptotrichia buccalis

(Robin 1879), Enlargement 20 000:1.

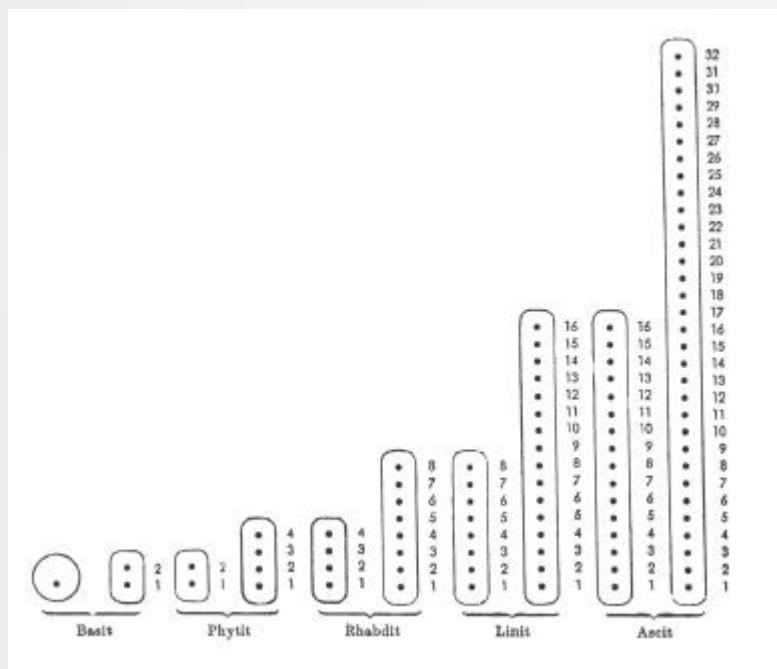


Fig. 1 - 6 Bacterium broteus Hauser, fig. 1 = basit stage, fig. 2 = phytit stage, fig. 3 = rhabdit stage, fig. 4 = limit stage, fig. 5 = catact ascit stage, fig. 6 = synascit stage (terminating into ascit on the top)



## 15. ANISOCYTOSIS

Diversities in the size of erythrocytes due to the pathogenic effects of the endobiont.

(Photos after no. 16).

16. POIKILOCYTOSIS+ ERYTHROCITIC-DEBRIS This comprises the manifold changes in the form of erythrocytes through the pathogenic influences of the primary parasite. One of the most frequently occurring deformations of erythrocytes is portrayed by a more or less ELONGATED, PEAKLIKE PROTRUSION of the erythrocytes which represent the transformation into a bacterial rod of the endobiont. This bacterial rod belongs to the phase of LEPTOTRICHIA BUCCALIS, which must be classified as the bacterial phase of the fungus *Mucor racemosus* Fresen. THE RELATIVELY SMALL FRACTIONS OF THE ERYTHROCYTES ARE ABLE TO REGENERATE. Poikilocytosis is characteristic for anemia.

## 17. DEGREE OF INFESTATION OF THE ERYTHROCYTES

This represents a very diversified matter, which must be directly experienced.

a: not infested

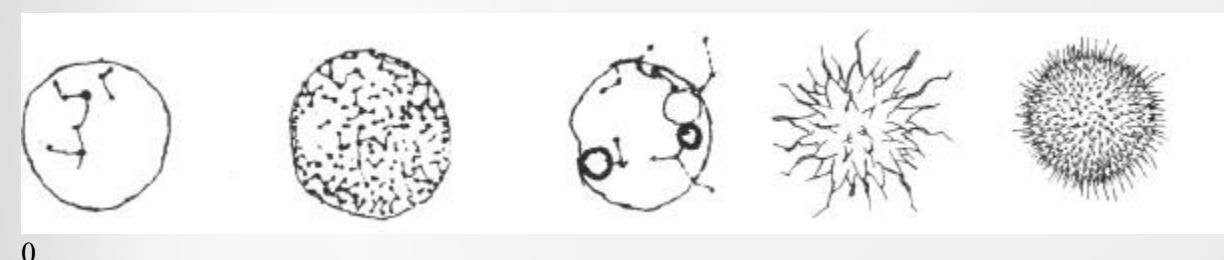
b+c: moderately to strongly infested

## 18. VALENCE OF THE INFESTATION OF THE ERYTHROCYTES

This refers to the VOLUME-ENLARGEMENTS of each parasitic form which can be found in the erythrocytes. (Figures and photos after no. 19).

## 19. VACUOLES OF ERYTHROCYTES

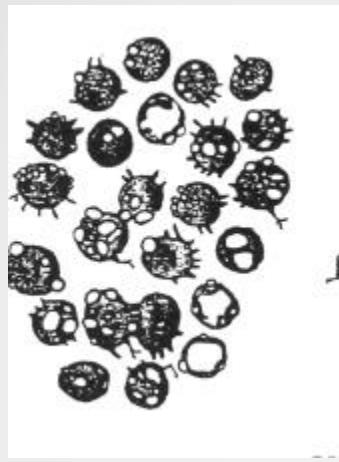
These are a sign of stronger, degenerative factors of a parasitic nature.



Erythrocytes with different valences:

From patient with metabolic disturbances and swelling of the liver.

Erythrocyte from cancer case. Live blood picture. Especially high valence endobiont infestation.

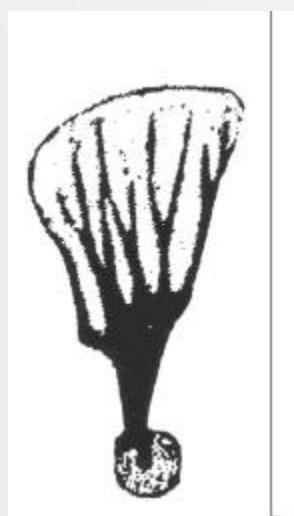


Erythrocyte with sporoid symprotits. Cholecystitis and hepatitis.

b+c: moderately to strongly infested

#### 20. DENDROID DEGRADATION OF ERYTHROCYTES

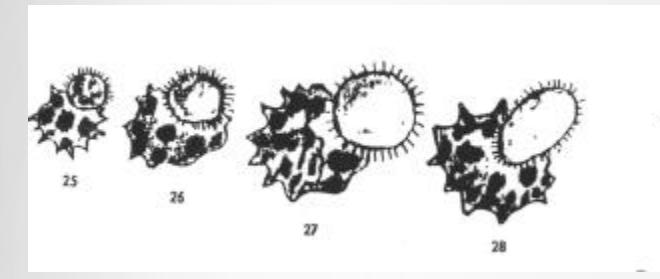
This tree-shaped or rope-like shaped parasitic growth form belongs among the ?fibrin? which school-medicine interprets as blood coagulation. However, these processes BELONG TO THE RARITIES in erythrocytes. Still, their presence is, likewise, a documentation of cancer, EVEN WHEN THEY ARE ABSENT IN LEUCOCYTES.



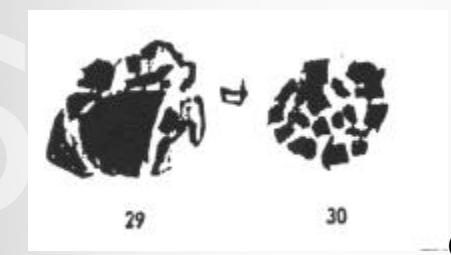
Erythrocyte with chondrit-net (fibrin) in particularly fine net work; including 5 sporoid symprotits. The rather exhausted erythrocyte also contains 3 sporoid symprotits. (patient with lung cancer)

#### 21. SCLEROTIC CHANGES IN THE ERYTHROCYTES

These are special manifestations that are particularly found in erythrocytes. Thus, THE TOTAL CONTENT OF THE ERYTHROCYTE may degrade into a large number of sclerotic CHUNKY AND CRYSTALLINE DRY PROTEIN PARTICLES.



Native blood examination. The four erythrocytes in the condition, that the dioekothecite leave them in ripe condition. The condition of these erythrocytes is a little bit plaque-shaped.



2 erythrocytes from the same blood, live blood, apparently after the dioekothecits left, strongly cloddy-pseudocrystalline.

#### 22. INFESTATION OF THE LEUCOCYTE NUCLEI

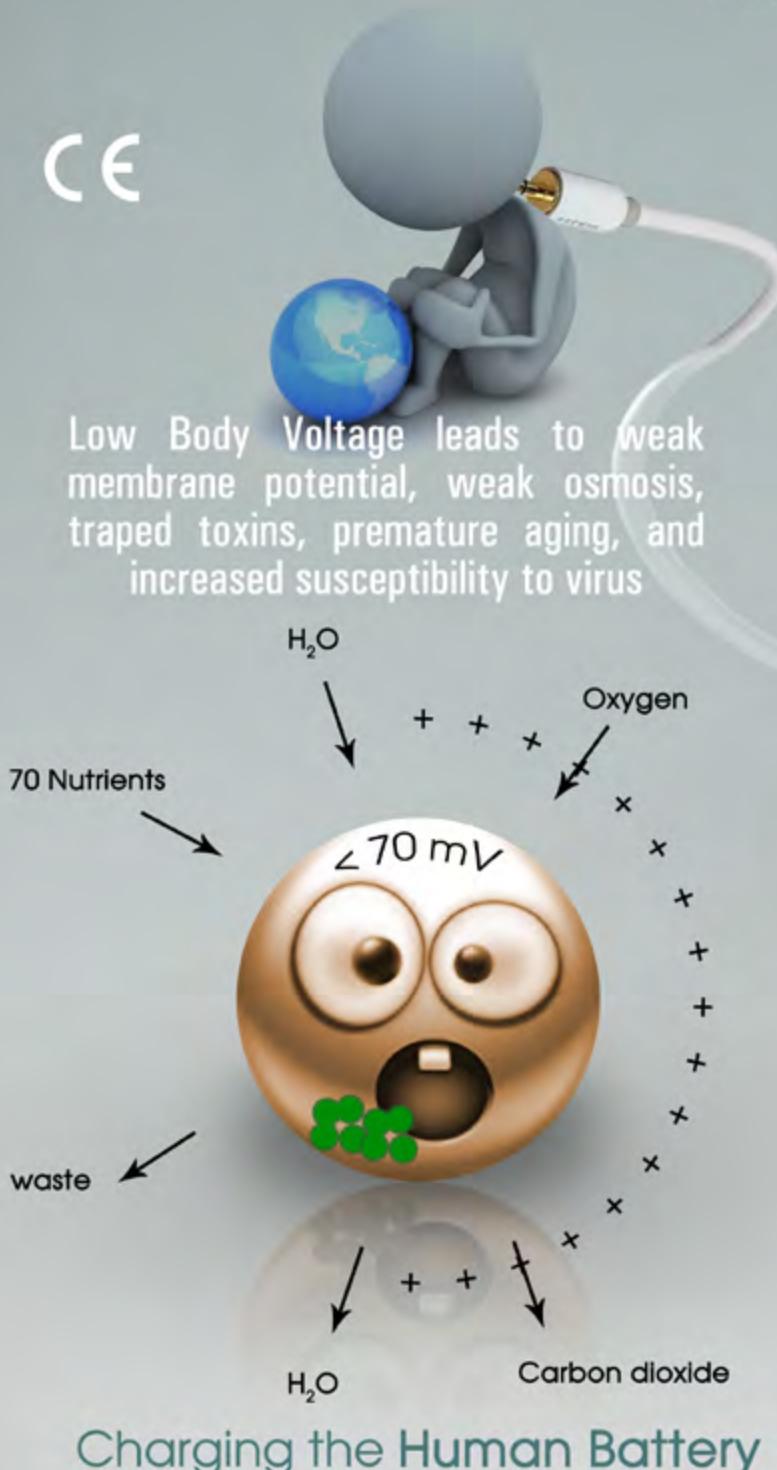
The parasitic infestation of leucocytes and lymphocytes is of extremely diversified nature. Essentially, the valences of the symprotits rise constantly; they can transform into a sporoid form, and finally reshape themselves into thrombocytes, which are able to fill up the entire nucleus. The rises can be designated as: very weak, weak, moderately strong, strong, and very strong. (Photos after no. 23)

23. INFESTATION OF THE LEUCOCYTE PLASMA The parasitic elements are found in the cellular plasma as symprotits, sporoid symprotits, and as thrombocytes or microthrombocytes. All of these are able to grow out of the cell on filum pedicles, or remain in the plasma itself in all these elemental forms. In Hodgkin, and even more in lymphatic leukemia, a very large portion of all leucocytes or lymphocytes can degrade into symprotits within their nucleus and plasma and these can further develop themselves into thrombocytes. They become fully filled up with these thrombocytes. Barely infested leucocytes may even prove themselves to be a rarity. THE SEVERITY OF THESE CASES CAN BE DETERMINED BY THESE MEANS.

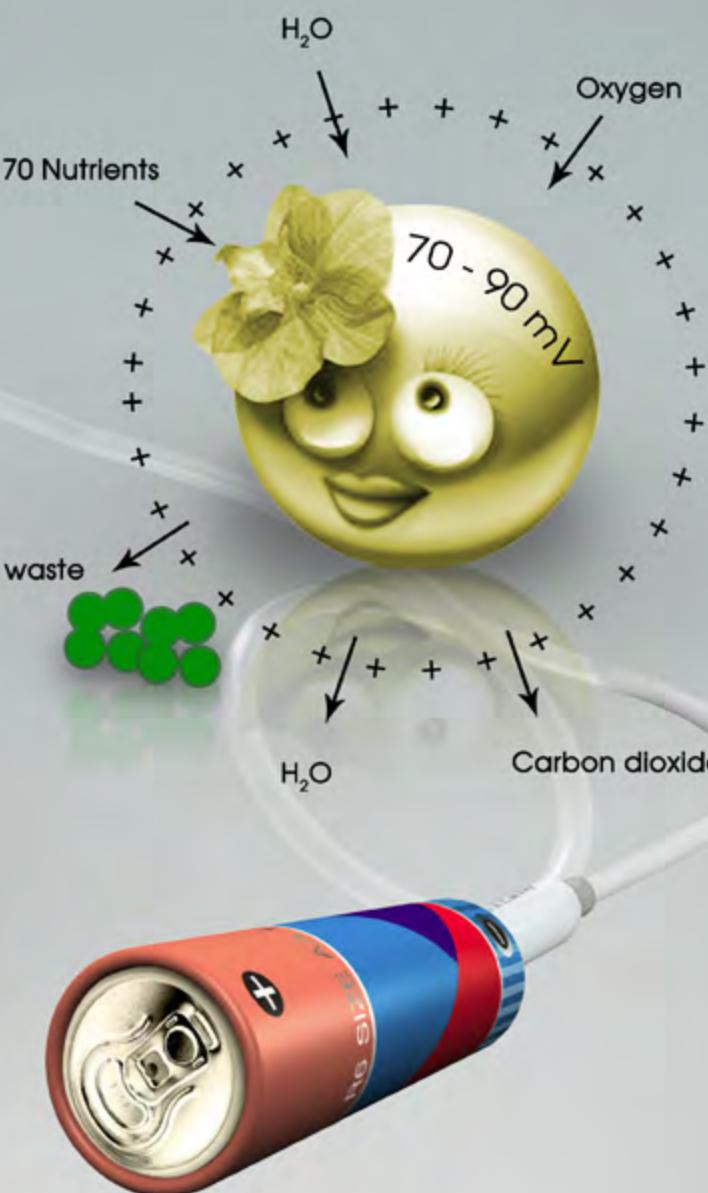
#### 24. DENDROID GRADATION OF LEUCOCYTES AND LYMPHOCYTES

The formation of tiny chondrit trees (= fibrin) of the parasite, can grow into ever stronger little trees, which grow far out of the cell and the nucleus. All this is valid for both leucocytes and lymphocytes. THE MANIFESTATIONS ARE CO-CHARACTERISTIC FOR CANCER, HODGKIN, ETC., BESIDES OTHER CRITERIA.

CE



Healthy membrane potential and adequate body voltage makes all of the functions of the cell work better



## Charging the Human Battery

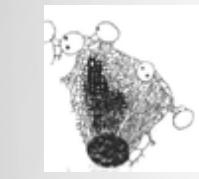
Factors that influence the body voltage and membrane potential are fatty acids in the cell membrane, minerals, especially salts, hydration water, oxygenation, stress, toxins and life style.

The SCIO has been proven in tests to increase the electrical potential of the body. Increased cellular membrane potential makes osmosis increase, which increases detoxification, nutrient transfer and absorption, hydration, oxidation, and all cellular functions in general.

If you need more information on the SCIO and purchase details please get in touch with us

**Maitreya Kft.**

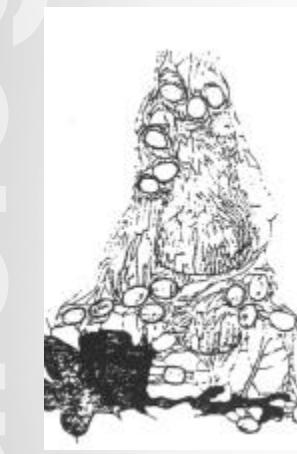
tel: +3613036043 | web: [www.qxsubspace.com](http://www.qxsubspace.com) | e-mail: [info@qxsubspace.com](mailto:info@qxsubspace.com)



Lymphocyte, completely destroyed by the endobiont. The nucleus is filled with chondrit forms and the plasma is dissolved by the filum-system into a tree like fibrin-dendroid. The latter copulates with the parasites which are enclosed in the nearby erythrocytes.

### 25. DENDROID VACUOLES

These come about by the fusion of thick ropes of fibrincords of the parasite so that more or less densely arranged holes (vacuoles) remain only in the larger open areas. They may be smaller or larger in size. THEY ARE A DOCUMENT FOR STRONGEST DESTRUCTION OF LEUCOCYTES OR LYMPHOCYTES.

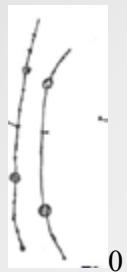


Below, dark symplast formed by numerous symplasts of leucocyte nuclei of endobiontic nature. The chondrit-dendroid stretches far over the slide and includes in this illustration 18 erythrocytes.

26. SCLEROTIC PARASITIC FORMATIONS These are dry protein organizations based on the direct fusion of living colloids (systatogeny), as with the endobiont and other parasites. They are always in the human body and, especially, in the blood. An ongoing characteristic of all these sclerotic formations is their capacity of tolerating a temperature of 310 degrees Celsius without the smallest damage to their capacity for life. One can also see on them the appearance of tiny germinating foci on the inner angles of these formations and on the outer corners, showing low-valenced chondrits, respective chondrit-trees in the change between filum and symprotit. Described in brief, they are classified as follows: a) Sclerotic, usually very long filum-threads (often

stretching over the entire visible field)

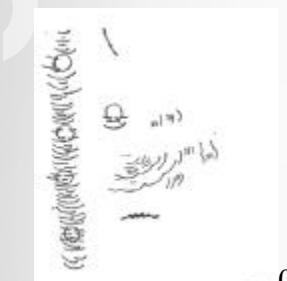
b) Very similar to these krypto-valent synascit threads



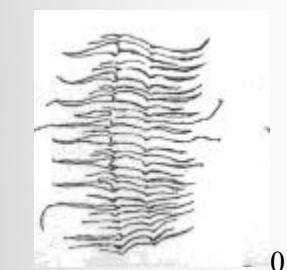
d) Sickle-shaped dry protein discs (drepanids). They arrange themselves most frequently in series, one behind the other, so that most microscopists rate them to be scratches in the slide.



- 0 Sclerosystate-drepanids from colloid material, sedimented by normal saline solution from a spore culture of *Aspergillus niger* van Tieghem.



The same from venous blood. Including 5 erythrocytes, which are partly penetrated by these forms (diabetes in 8 year old boy).



Sclerosystate-drepanites sedimented by normal saline solution from *Aspergillus niger* van Tieghem spores.

e) Fly-shaped dry protein formations (pteroharps). They are predominantly found in higher endobioses.



*Aspergillus niger* (van Tieghem), created from spores through addition of 5% soda solution, forms 2 fila with symprotits and thecits, which show a fairly amount of mych (primary nuclei); Enlargement approximately 5 000:1.

c) Pseudocrystals:

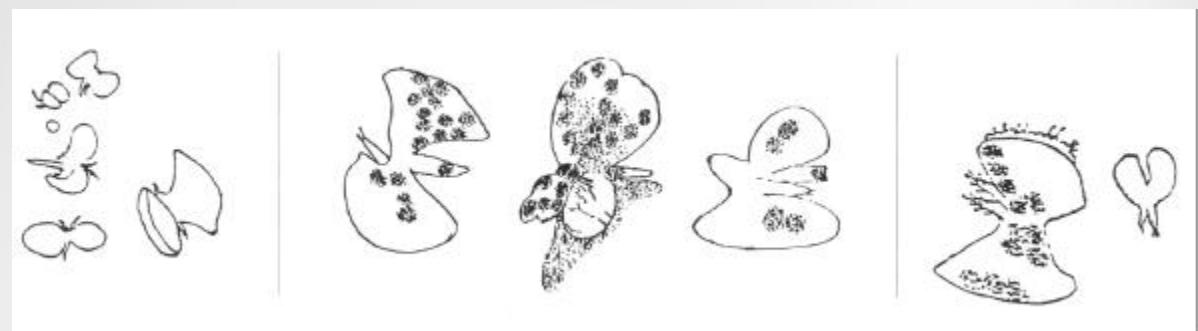
In the form of needles or angled plaques (chondrits arising from the corners)

Pseudocrystals of the endobiont with systatogenetic nature together with the poliomyelitis-parasite. These so compelled ?pseudocrystals ? are a double-nature.

Blood examination from horse. Sclerotic forms (false crystal forms). Bornaic illness.

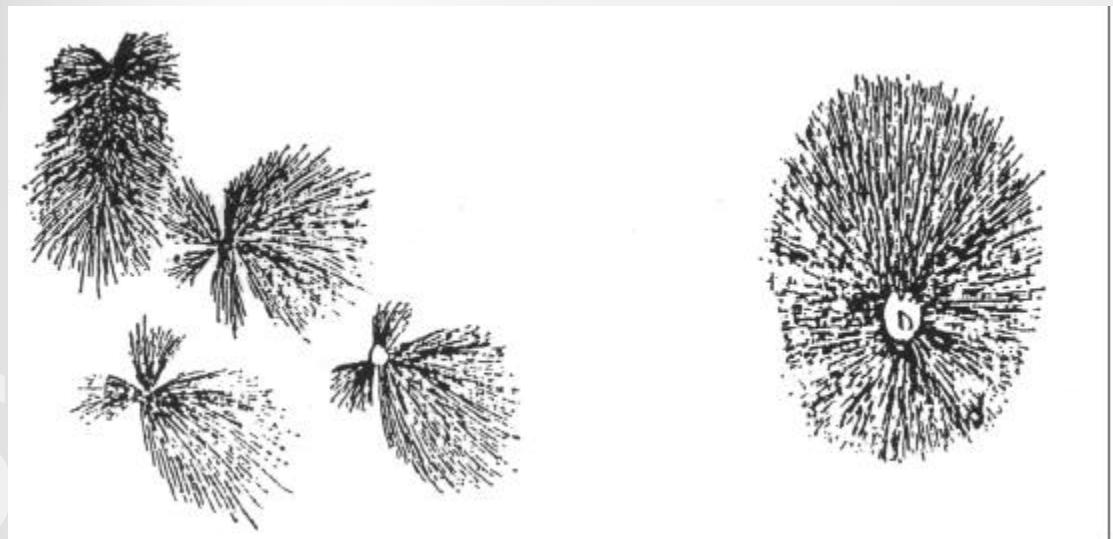
The wider synascit right is lamellar. Between also bigger sclerosymprotits.

The single parts of the sclerotic synascits (pseudocrystals) are put together catactically, so they seemingly have a crystal needle appearance.



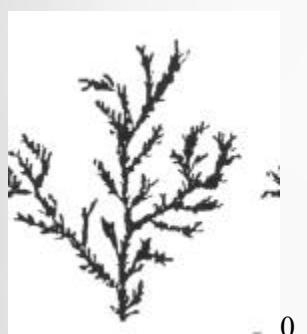
0  
Pteroharps from vem?puncture of a patient with intestinal bleeding and asthma.

f) Plumelike dry protein formations (ptylosclerits)



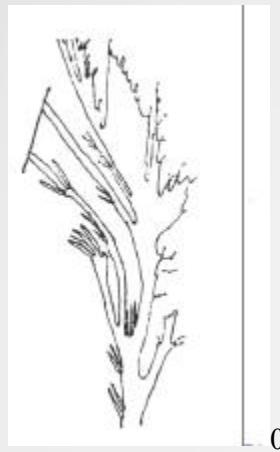
0  
Plumed systases under addition of 5% soda solution. The same originating from a colloid-thecit.

g) Moss-like sclerotica (bryosclerits)



0  
Aspergillus niger van Tieghem from spore material with normal saline solution. Moss-like sclero-systasis formation.

h) Fan-shaped sclerotica (rhipidosclerits)



Colloid masses concentrated in water (1 1/2 year old) through addition of 5% soda solution for lamella-like sclerotic formation.



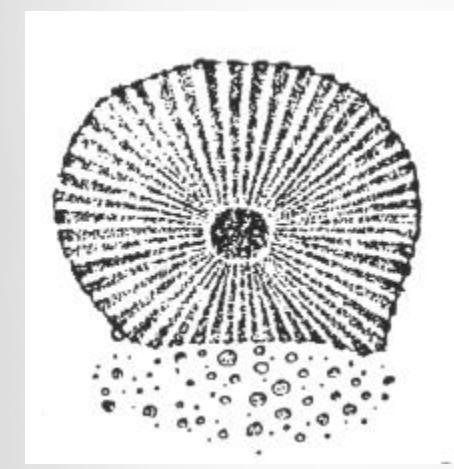
Lamella-like sclerotic formation, developing by gradual drying out of the plumes of the *Mucor racemosus* Fresen colloids. This occurred beneath the cover slip. To the right 4 flat sclerotic structures, of which the lower most one at the left shows a pteroharp.

i) Cross-shaped dry protein formations (chiosclerits).



Bouillon culture of *Aspergillus niger* van Tiegem + ? part of soda solution 5 % systasis occurs during the process of drying out cross like arrangement of systases out of living colloids. In the 1. illustration, top to the left one can recognize the clodlik systasis. In all the different 9 systases one sees the change from pteroharp to these cross-like structures, systases occurs during the slow drying out.

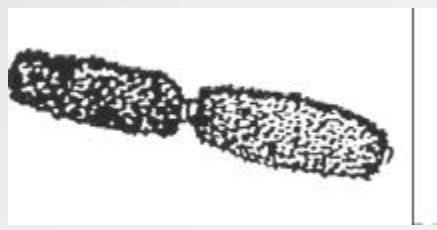
k) Sclerosymplasts. This group contains manifold formations of bubble-shaped, disc-shaped, to plane-shaped nature. They are keratinoses in pseudocrystal form (?Scare shapes?).



Radial double sided sclerosymplast of the endobiont in heteroncytasis with the systatogenetic influences of the infectious agent of poliomyelitis.

## 27. DEROSONASCITS

A larger group of sclerotic formations. The derosynascit is a sclerotic formation that is more than double the size of an erythrocyte (in lymphatic leukemia, Hodgkin, warts).



Two still connected derosynascits from Hodgkin blood. These are characteristic for lymphatic leukemia, Hodgkin, can however be found occasionally in the secretion of hard verruca. Their building material consists mainly of sclerotic elements of the endobiont.

#### 28. SYMPLASTS

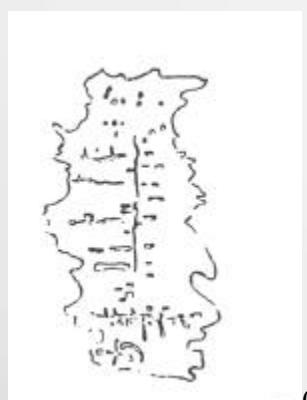
These relate to the agglutination of all developmental phases of the ?Virusphase, bacterial phase, fungal phase series.? It is NOT a developmental stage but a creation due to the urge for unification (symplasm), which can be built up in the very shortest of times in a fraction of a second.

#### 29. THE SYSTATOGENY

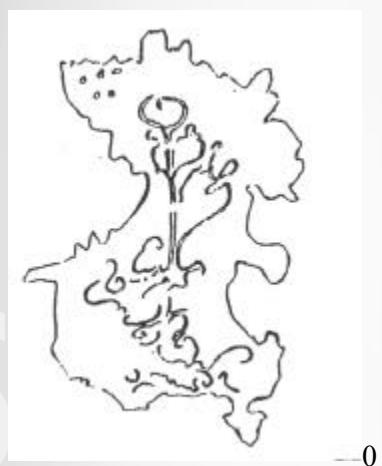
relates purely to the direct unification of living colloids amongst each other. It is pH-dependent. (Protit-veil, colloid-thecls). These final living units (colloids), with a diameter of about 0.01 ~tm, are able to be formed within the shortest time, a fraction of a second.

Because the pH-factors are of essential significance for the systatogenetic orchestration of nature, a few examples of nature's play are discussed from this perspective, on the basis of the following illustrations.

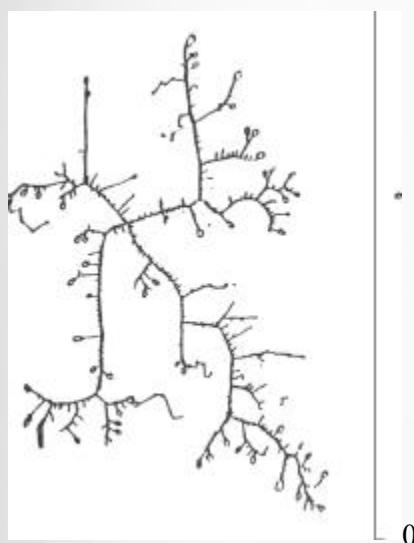
First of all, there is the phenomenon of the protit veil. This accumulation of colloids is entirely dependent on the highest possible pH-value. They develop into more or less limited formations representing that form of the developmental processes of microbes which are covered under the term COLLOID-THECIT. In the GIEMSA dyeing process, they take on luminous blue coloring. Forms, 4 or 6 - radiallyzed, are quite frequent. In Fig. 12, nearly all developmental forms of the primitive phase and also of the THECIT, the ASCIT and - in the widened area below, on the right - the SYNASCIT are represented. In the synascits one can notice also numerous SPOROID SYMPROTITS that take over the role of the mych. At this point I wish to remind you that every developmental phase is capable of producing all the other developmental phases.



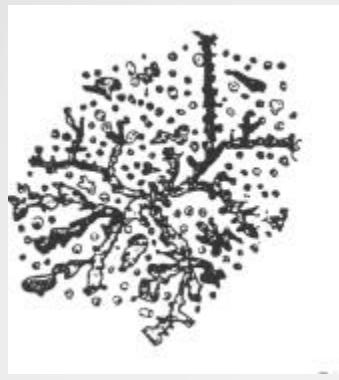
Patient with leukemia & Hodgkin. Outside the blood smear emigrated colloids, which arrange themselves in a systatogenetic manner to a colloid thecit. The resulting fissures are arranged in a straight line or 90 degree angle.



Another view of the same sample, the fissures are curved and embracing.

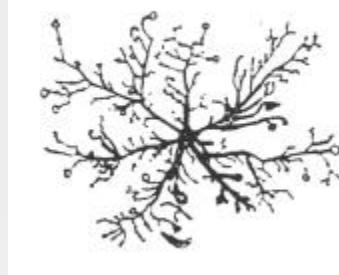


4 Radiate -filum-star, systatogenetically developed in patient with pulmonary cancer, however, belonging to the endobiont. Unstained. In the zone at the edges of the slide, free of blood and outside the smear. Purely of systatogenetic nature. The ovoid, sporoid symprotits are especially shiny.



- 0

Systatogenetic construction complex from smear on non-provided halos of the slide emigrating colloids.



- 0

#### ANNOTATIONS CONCERNING THE BLOOD EXAMINATION

The blood for this examination must be always drawn under the same conditions, best in the morning on an empty stomach, to avoid a confusion with the food-chylemia. It is in principle indifferent from which part of the body the blood is taken. It is only important that the blood appears spontaneously; it may not be squeezed out because then superimpositions and distortions of the very sensitive erythrocytes take place which forestall a perfect assessment respectively lead to false conclusions. A small drop of the patient's blood is put on the slide and protected with a cover-glass so that it spreads out up to the edge of the slide without exerting any pressure on it.

Slide and cover-glass have to be free from dust and grease. Now and then they also have to be examined on production inclusions because those can resemble endogenous depositions. The cover-glass should not be too small, best is a size of 24 x 48 mm. This size has a sufficient weight to effect a well-proportioned distribution of the blood on the slide. At the same time it leaves enough free space to be able to observe a possible systatogeny. Moreover the immersion oil does not mix with the blood.

Advice: Take the drop of blood directly with the cover-glass and put this immediately on the slide. Take a drop of blood with the cover-glass at least two times. The assessment is then more reliable and if one smear gets lost due to awkwardness, you still have one smear in reserve. Moreover you can stain one smear *?natively?* to compare it with the unstained smear.

To get the safest results, examination should take place immediately because the sensitive endobionts can change their form and valence *very* quickly by changes of the pH in the drop of blood, due to reasons of time.

If the preparation should be examined for a longer period, it is possible to seal it with liquid paraffin to avoid

a drying up.

As Mucokehl injections cause a degradation of higher stages of the endobiont into lower ones, the blood appears slightly milky or cloudy after 24 hours. This cloudiness, the *?protit veil?* consists of the smallest developmental stages of the endobiont. The protit veil disappears after a few days by elimination, especially by a good elimination therapy for example with homoeopathic remedies or with a diet or even better with an injection of the Mucokehl excretion serum. For this reason a repetition of the Mucokehl injection should be only effected after one week at the earliest.

Blood Examination Report No. ....

pre- and surname: ..... date of birth: ..... street: ..... city: .....  
attending physician: ..... diagnosis: ..... blood sample from: ..... preparation: .....  
coagulation: ..... serum: .....  
.....

1. protit-veil:
2. colloid-thecit (cell without nucleus, native): 3. filit-phase (in darkfield):
4. symprotitit-phase: 5. macrosymprotits: 6. sporoid symprotits: 7. spermits in darkfield (synonym: bacteriophages): 8. free chondrits:
9. colloid-symplasts:
10. mychits (bacterial spheres):
11. thrombocytes, microthrombocytes: 12. thecits:
13. bacterial rods + ascits: 14. synascits:
15. anisocytosis:
16. poecilocytosis + erythrocytic debris: 17. strength of erythrocytic infestation: 18. valence of erythrocytic infestation: 19. vacuoles of erythrocytes:
20. dendroid degradation of erythrocytes: 21. sclerotic changes of erythrocytes:
22. infestation of leucocytic nuclei: 23. infestation of leucocytic plasma:
24. dendroid degradation of leucocytes: 25. dendroid-vacuoles:
26. sclerotic parasite formations: 27. derosynascits:
28. symplasts:
29. systatogenetic processes: Total Evaluation:
30. valence of the endobiont: 31. evaluation of the endobiosis: 32. remarks:

In connection with the blood examination form I wish to point out the following:

according to Prof. Enderlein

1. The PARACOLI BACTERIUM is not a degenerated coli-bacterium, but the phytit-stage of the endobiont.
2. The causal reason for the INFECTIOUSNESS of FILTRATES OF TUBERCULOUS MATERIALS is the chondrit-stage of the tubercle bacillus. This was noted as early as 1910 by FONTES (Brazil).
3. H. DOSTAL has also proven the easy trans ferability of the tubercle bacillus into the sphere (basit-stage) by GROWING it in a liquid broth.
4. FIBRIN is by no means the sediment of a protein coagulation, but it is the chondrit-dendroid of the endobiont.
5. THROMBOCYTES are no blood organelles (platelets), but they are thecits of the endobiont.
6. MEGAKARIOCYTS (Metschnikow) are no normal cellular elements but they represent the lost ability of cellular and nucleic division due to massive infestation of these cells by the primitive phases of the endobiont. These cells have been forgotten over the eager attempts towards solving the focal problems in the sanitization of the ?marrow of all bones. ?
7. The NUCLEIC CHAIN CELL has reference to the just quoted, only, in this situation, the nucleus still has the capacity to divide, while the cell has lost it. 8. The MEGALOBLASTS of pernicious anemia do not represent erythrocytes which contain nuclei, but erythrocytes that contain a colony of endobiont chondrits, which get blown up to abnormal size by these (pseudo nucleus!).
9. NORMOBLASTS are erythrocytes stemming from the bone marrow do not have a nucleus but only a pseudo-nucleus, consisting of a colony of endobiont chondrits.
10. MACROCYTS. Abnormally enlarged erythrocytes without ?pseudo-nuclei?, their enlargement being likewise due to a massive infestation with the chondrit-stage of the endobiont.
11. MARGINAL GRANULES of the erythrocytes are no organelles (Schilling) but they are symprotits of the endobiont.
12. MARGINAL RODS of the erythrocytes are no organelles (Schilling), but they are bacterial rods of the bacterial phase of the endobiont, which arose from the just quoted marginal granules. Later on, they free themselves and crawl upon the erythrocytes and leucocytes like cater pillars (wherefore Sanitary Counselor Dr. med. Otto Schmidt of Munich named them ?worms?).
13. Also the ROUND and SPINDLE CELL SARCOMA contain no round and spindle cells of the host, but these are cross-sectioned (round) cells and obliquely cut (spindle) cells of mycelia of the endobiont.
14. RETICULOCYTES (Heilmeyer) are no erythrocytes with special organelles but erythrocytes infested with endobiont chondrit trees in their interior.
15. PSEUDOPODIAL FORMATIONS IN THE LEUCOCYTE (dendrites) (according to BOND, London 1924: ?The Leucocyte in Health and Disease?, H.K. Lewis & Co.) are, in fact, chondrit-dendroids of the endobiont. According to the doctrine, they are also described as ?Fibrin?!

16. STERILITY OF THE HUMAN BLOOD (both in the sediment and in the filtrate). This illusion within the doctrin is, in fact, a massive infestation of all blood elements in all vertebrates, including the human being. Yes, even the healthiest human being is ridden with the primitive phases of the endobiont, and this infestation leads through genetic development to the bacterial and even to the fungal phases, when there are increasing disease conditions.

17. STERILITY OF THE BLOOD SERUM is an illusive doctrin concerning the contents also of the serum, which contains most diverse primitive phases of the endobiont.

18. DIAPEDESIS is the illusive doctrin concerning the process of a scrambling of all protein substances within the human body by the endobiont and its formation into ?fibrin?, at the time of exitus (death).

19. THE CULMINATION OF THE FUNGAL FORM (Mucor racemosus Fresen) of the endobiont can easily be obtained through cultivation out of tumor cells. This has been proven as early as 1903 by Sanitary Counselor Dr. med. Otto Schmidt (Munich), as also subsequently, by myself.

20. The CALCIUM SHELLS OF TUBERCULOUS FOCI in the lungs are not protective processes by the host, but phenomena of calcinosis due to FAULTY REGULATION, set up by the endobiont for his own protection against the defensive capacity of the human blood.

Professor Pierre Delore, of the medical faculty in Lyon, who was well aware of the consequences of the ever increasingly catastrophic effects caused by disrespecting the natural laws and biology, summarizes his conviction in the following words:

THE SCIENCE OF HEALTH IS PREDOMINANTLY A CONCERN OF BIOLOGY.

?Consecutio sine quo non?: The health concerns of human beings comprise two gigantic FACTORIAL AREAS:

The one FACTORIAL AREA is the ATTACK FROM OUTSIDE through the environment in its largest context, among them also the parasites of the most diversified varieties; they INTENSIFY INTO INFECTIOUS DISEASES AND EPIDEMICS. In this area, surprisingly much has already been accomplished by medicine through hygiene and according to Virchow, even without having the faintest idea of the developmental microbiological processes. The reason for these processes lies in the biological fact that the parasitic microbes are mostly present only in a single developmental stage of the totality of end less varieties of developmental series.

The second FACTORIAL AREA, however, is a most internal matter of SYMBIOSIS between a HUMAN BEING - along with all other vertebrates - and ENDOBIONTS (Mucor racemosus Fresen/Aspergillus niger). In this symbiosis, existing over millions of years, especially the ENDOBIONT Mucor racemosus has been exceedingly successful in breeding many hundreds of developmental phases capable of nearly limitless manifoldness of pathogenicity, so that ONLY A COMPARATIVELY SMALL NUMBER OF NON PATHOGENIC STAGES REMAIN THAT DO NOT HAVE A TRACE OF PATHOGENICITY. Among these is, especially the last primary unit, the COLLOID (= PROTITIT PHASE), as well as the subsequent, low-valenced CHONDRIT STAGE and the final culmination, the spore-forming FUNGAL PHASE.

Before considering the isopathic foundation of treatments, I want to emphasize the following: In the RECOGNITION of the nature of this catastrophy, namely, the catastrophically RISING OPPOSITION of the human being towards this primary symbiosis having lasted hundreds of millions of years within the totality

of all vertebrates - lies also the path for an aimed resolution of these processes. It is the isopathy. For this purpose, isopathy uses LIVING COLLOIDS in a fully united and simple way, which must be brought to the scene merely by the slightest modification of the pure mechanical differences of diverse disease symptoms belonging to a unique DISEASE COMPLEX. This disease complex is simply the ENDOBIOSES, the addiction of CONGESTION.

The parasitic nature of the causative factor for all chronic diseases, including cancer, Hodgkin, etc., which has infested all vertebrates in their total development so extensively that no one single cell has remained untouched by this monster throughout the ages, is a unique occurrence, which is surpassed by yet another: the PRIMARY SYMBIOSIS with the limitless abundance of its hosts.

Here, I want to bring into remembrance that the human blood is considered sterile to this very day! The path of elimination for degradation products is in every healing process through the skin, the bladder, the intestines and the bronchies. To these belong also the interior foreskin of men and the vagina of women, that is, the epithelial organs and, in a form of apathogenic phases, with the SINGULAR EXCEPTION OF THE INTESTINES, in which degenerative phases are able to reconstruct themselves into short rod forms, which can have an extremely dangerous action of strong obstipation facilitating the further course of cancer; they are, by no means, degenerated coli-bacteria. Dr. med. Harvey BLANK (1956) assigned the name MONILIASIS for a new disease-complex that has become better known in more recent years and which is based on apathogenic endobionts that have been stimulated into pathogenic action through antibiotic drugs.

There is no doubt that what is termed an INFECTION is entirely out of the question in the unique occurrence of a primary symbiosis with a primary parasite in all chronic diseases including cancer. Of all the many hundreds of forms that the chronic disease complex manifests, there is no one that has ever been observed as caused by an infection. An infection with living material having the purely microbial nature of these primary parasites (endobionts) would only result in the meager remnants of the apathogenic phases (REGULATORS) attacking these foreign intruders; the extremely primitive phases of the sperms would copulate with marginal primary nuclei (mych) of the primary parasite and dissolve these into the chondrit stage of primitive valence.

Upon clear contemplation, not only the cancer problem but the entire pathology, as taught by school-medicine, have become unsustainable. In any case, it is extremely revealing of the insight that Prof. Sauерbruch, in allowing a series of cancer patients to be treated isopathically in his hospital at the Charite and who, subsequently, in the closing years of his life again and again had pointed out that: ?IF ENDERLEIN IS CORRECT, THEN WE CAN THROW OUT OUR ENTIRE LITERATURE? or, alternatively expressed: ?THEN WE CAN PACK UP?

Now, we come to the burning question about infectious diseases. For these also, the identical basis of complete ignorance concerning the entire biological developmental conditions and the developmental construction of all microbes in the area of fungi, bacteria, and primitive phases exists. Because the VIRUS STAGE predominantly involves but a single developmental stage, which can be located only in a particular place of the total cyclic range of developmental forms as PRIMITIVE PHASES (to which the so-called virus belongs) - BACTERIAL PHASES - FUNGAL PHASES, a factor has slipped into the monomorphistically oriented doctrine which ultimately serves the final outcome. (Success of sanitary measures.) One exception here is e.g. the typhus pathogen. Its bacterial form causes the main disease symptoms in the intestines, but after its disappearance from the intestines, it leaves behind primitive forms of colloidal or, at the least, ultramicroscopic remnants within the blood, through which the type of intestinal infection can possibly be identified by means of agglutination tests, weeks or even months after the recovery.

However, in contrast to epidemics and infectious diseases, an entirely different situation prevails for the complex of chronic diseases. The purely biological understanding that the primary infection of all the vertebrates with the endobiont MUCOR RACEMOSUS FRESEN occurred at a very early point of the development of vertebrates, hundreds of millions of years ago - explains the unusual and gigantic development of the primary symbiosis. Simultaneously, with this genesis of a primary symbiosis, a shift of the VIRUS STAGE onto most of the thousands of developmental phases in the endobiontic development has occurred.

Each of these innumerable series of pathogenic forms of the cycle of a singular microbial species has succeeded not only in diverse valences or sizes and developmental levels, but also in an unimaginable differentiation not only in the level of pathogenicity, but also into a nearly inconceivable differentiation into thousands of chronic diseases with diversified disease symptoms, which give a distinctly different disease appearance. Yet, all these diseases are able to blend into each other gradually, so that cancer makes itself known as rheumatism 12 - 15 years earlier; a stomach-ulcer terminates into cancer; leukemia develops into a case of Hodgkin and vice versa; and thousands of other unusual and surprising characteristics, can develop.

All these biological, purely CAUSAL FACTORS stand in contrast to the CONDITIONAL FACTORS. These cancerogenic and dietetic factors as contributory, conditional causes have become more and more expanded so that their number nowadays exceeds one thousand, by far.

#### THE PREVAILING AND MOST ESSENTIAL FACTORS, HOWEVER, ARE THE FUNDAMENTAL DIETETIC ERRORS.

The nature of the dietary error consists in the fact that the primary parasite in the body, the endobiont is fattened into higher and higher developmental phases through habitually eating too much protein from animal and also plant sources, especially through the intake of meat, fish, and white flour products; the higher stages simultaneously are connected with higher and highest pathogenicity. The preference for COOKED FOODS also contributes to this. According to Enderlein, VEGETARIAN RAW FOODS alone are the foundation for total health. (We may not forget that the endobiont is a colloid of PLANT ORIGIN.)

Numerous doctors everywhere confirm that cancer can be healed by Isopathy based on living colloids (= protit stage) of the causal factor. All this proves with absolute safety that only by the replacement of COLLOIDS lost through the diets of civilized countries, the healing processes can be initiated and accomplished. This ?replacement? relates, in the case of cancer, to the just mentioned LOST COLLOIDS.

Thus, let it be first summarized that the healing possibilities of cancer rest singularly within the possibilities of a primary symbiosis with a primary parasite, accomplished since primary times, and a purely BIOLOGICAL replacement of regulatory parts of its cycles that have become lost through our pseudoculture. All this lies outside of - let us say - schoolmedicine's therapy.

It is a most disquieting paradox that we fight diseases with medications, which simultaneously destroy the defensive mechanisms of the body. We can even add to this that it is not merely a case of destroying the defensive mechanisms, but even more, a case of overfeeding the worst hereditary enemy of humanity.

For this therapy, it is to be particularly pointed out that - just as Prof. Dr. med. Friedmann considered it a requirement for patients healed through the turtle tubercle bacillus (today Mycobacterium phlei = UTILIN ?S?) to receive additional injections every 3 months for their health maintenance such follow-up, likewise, remains necessary to a higher degree after the healing of all serious ENDOBIOtic DISEASES, and particularly those considered to be ?incurable?. Not only is a subcutaneous injection of endobiont-chondritin (Mucokehl) urgently necessary every quarter of a year, but also the strictest raw food diet must

be maintained at least for several years. In all serious endobiotic diseases, such as cancer, Hodgkin, leukemia, the danger lies in owing the genes of the dangerous phases, and with them also higher and highest pathogenicity, the primary parasite constantly persists inside the human body. Thereby, the increased tendency to create highly pathogenic forms always makes itself felt when the opportunity is offered for overfeeding itself with protein.

This is entirely in contrast to all epidemic and infectious diseases. What helps here is only the regular weakening over months, or better weeks, by absorbing through rubbing in of uncountable billions of absolutely apathogenic colloids consisting of primitive phases or colloids, which have been cultivated outside the human body and beyond the culmination. Even better is an injection every 3 months.

**What is nutritional microscopy?** It is the use of a specially configured video microscope within a health care practice. The microscope is hooked up to a video camera, which goes to a TV monitor for easy viewing. It is used first as a tool for the health care practitioner to gain insight into a patients metabolic and nutritional status. It lends assistance in determining what types of nutritional supplements would be optimally correct for the patient. Secondly, and possibly of even greater importance (and certainly it has been shown to have the greatest impact), the microscope is an educational tool for the patient. Few individuals have ever seen their blood live and up close right on TV. Blood is the river of life flowing through each of us. As human beings, we all inherently understand this. When a person sees their blood for the first time, they realize that there is dynamic activity taking place within. They begin to understand at deeper levels the need to take care of their health. It has consistently been shown that subsequent patient compliance with the doctors recommendations is greatly improved.

As a side benefit, using the microscope often increases patient referrals. It is unique. It is real. Patients love it and they send their friends. It is also a tool to give dynamic, one of a kind group presentations for practice building.

**What exactly is a 'darkfield' microscope?** A darkfield microscope is simply a standard laboratory microscope, to which certain optical techniques are utilized to transform how light comes through the specimen being viewed. For example, let's say we are viewing live blood on a glass specimen slide. The normal mode of a microscope is called 'brightfield'. In this mode of viewing, light shines straight through the specimen. When light shines straight through a specimen, transparent objects are invisible. It's as if you were standing to the side of a sunny window gazing through dust. If there was a white wall between you and the dust, you'd never see the dust because it is transparent when trying to be seen against the white wall. However, if you put a black curtain where the white wall is, all of a sudden the dust pops into view. The darkfield microscope does the same thing. The specimen sits over a dark background (or field), and light is angled onto the specimen from the sides. Things that were once invisible now come into view.

**What is a 'phase contrast' microscope?** This is another way to view live blood for nutritional work. With this lighting technique, the light coming through the specimen is altered so that a portion of the light is shifted slightly out of phase with the original. The light now strikes the specimen and lights up invisible particles while also giving shades of gray. This is an excellent way of viewing blood for nutritional screening.

**Can I diagnose disease with this technique?** No. The microscope as we use it is not a diagnostic tool, but a powerful window to view the action of the body's metabolic processes on the most important of body fluids.

**How can your company help me get started in this area?** We provide the nutritional/microscope training classes as well as the microscope systems for your clinic.

**What techniques will I learn/use for blood analysis?** When we view blood for nutritional counseling, we can use three primary techniques. The first two techniques view blood in its live, unchanged state. First we are looking at the overall terrain or environment of the blood with knowledge of the pleomorphic theories of disease as related to pH utilizing the European/German research. Second we can view blood from the more Americanized allopathic/nutritional perspective. In either case we are looking at what's normal and what's not. Red cells, white cells, T cells, B cells. Are there parasites? How fast is the blood deteriorating? This gives us insights to nutritional metabolic conditions. A third test we can perform is a dry layer test. Here we take a series of blood drops and let them dry on a specimen slide. The reasons for this is that the coagulation cascade of the blood gets thrown off when the body degenerates through oxidative stress, mycotoxicoses, or disease. This test can be very revealing, and it can give direction into what further tests to be performed.

**What does your nutritional/microscope training program cover?** It covers everything you need to rapidly begin an adjunct nutritional/microscopic service in your office.

**Do I need to be a licensed health care practitioner to take the training?** No. We often train clinic assistants and we start from square one with a dynamic overview and pre-training of health concepts to prep everyone in class.

**Why is pH taught in the pre-training workshop?** Understanding body and blood pH is *absolutely essential* to understanding what goes on in the blood. You cannot have a blood class without thoroughly learning pH concepts - unless you desire to learn only half the story. pH (concurrent with redox) controls everything that happens in the body; enzyme function, vitamin and mineral assimilation, electricity flow, parasitic formation. Metabolic body balancing and blood work cannot be done without an understanding of pH.

**Why is the lymphatic system taught?** The lymphatic system is our 2nd circulatory system. The lymphatics parallel the blood stream everywhere the blood flows. The blood stream and the lymphatics completes a circuit for blood protein circulation in the body. The live blood analysis gives insights as to what is happening in the blood, and the dry layer analysis gives insights as to what is happening in the lymphatics. Looking at live blood under the microscope is just a portion of what you can do with your microscope. Looking at the lymphatics through the dry layer technique furthers your analytic capability - and furthers the services you can provide your patient.

**You talk about further services to my patients, how can I use microscopic analysis beyond nutrition?** Let's say you complete a dry layer analysis and you learn that your patient's lymphatic system has poor circulation (this is something you could discover with the dry layer test). This is an opportunity to introduce lymphatic drainage massage, associated ozone steam baths, etc. into your practice. This area can be a stand alone profit

center that brings positive health results to your patient by helping them detox, as well as providing new revenue to you either through your own hands or that of a massage therapist. Likewise, the dry layer test could reveal a colon in serious need of a clean up. This could open an avenue for a colonic therapist or a strong reciprocal referral arrangement. These are just two examples. The different blood analysis techniques you will learn will be giving you insights to directions to choose for your patient's health that are in addition to nutrition. We cover some of these areas in class.

**Will you cover the nutritional products I use?** Yes if you desire this. You specify the nutritional products you use in your practice, and you will learn how to use those products in relation to your findings. If we are training you for a specific company, that company's products will be covered.

**How large are your classes?** Our training classes are small and very personal. On average, 4 to 8 students per class (12 maximum) and it will typically be held at a clinic, or in a home. This gives you very personal attention and it is one reason we can teach you as much as we can in 3 days.

**How much does this cost?** The cost varies depending on whether you have the instructor come to your clinic, or you and your staff come to Chicago. The microscope set up in itself is under \$4000, and if money is an issue, we can tinker with the hardware to get it under \$3,000.

**Is your training the only training I will need?** After the 3 days of training you'll be up and running and can be generating revenue with your microscope. However, once you embark on using the microscope, the training really never ends. It is on-going every time you look at a new blood sample. Live blood is dynamic and ever changing. Expanded classes on specific topics are an option you can choose for the future, but you'll get so much from our time together, it will keep you going for a while.

**Do I need a special license to use a microscope?** No. The microscope is only a tool. You don't need a license to operate this tool. What you say to people when you're using it is a different matter. If you are stating a diagnosis through its use, then you would fall under the specific medical licensing of your state. Likewise, you don't need a license to prick fingers in most states. But some states could consider it the drawing of blood which requires licensure, either nurse, doctor or phlebotomist. If you lived in a restrictive state, you could have patients prick their own fingers with the automatic devices diabetics use everyday. With restrictive (and largely unconstitutional) government oversight in the health arena today, we will cover legal aspects that you should be aware of as a healthcare practitioner working with the public.

**How can I use this knowledge if I don't have a health practice?** Some individuals who take this training do not have health care practices but are simply interested in the work because it is very exciting. Some of these individuals get microscopes and some don't. They attend for the education alone which is very unique. They co-op with others to share the cost. They

use the knowledge with family and friends. Some individuals are distributors for nutritional supplement companies and they use the microscope for group educational programs. Some work for doctors. When you attend the training you get a very dynamic program that can be used as a health seminar/workshop. Used with the video microscope, it becomes a highly visual, high impact program that people remember, and act on.

**How do I get started?** All arrangements can be made and further questions answered by simply contacting us.

## FRESH BLOOD ANALYSIS ACCORDING TO NAESENS

### A. WHAT THE ANALYSIS IS

The Naessens Fresh Blood Test is a preventive screening tool designed to permit the health practitioner and the person to observe transformations of the blood cells before the appearance of clinical signs. (This may be 18-24 months prior to clinical symptoms)

### B. WHAT THE ANALYSIS DOES

This analysis is not designed to be a diagnostic test, it cannot detect specific diseases. It does however, detect the progressive weakening of the person's natural defenses or terrain, which includes the immune system.

### C. WHO DOES THIS ANALYSIS?

This analysis is done by a person qualified in somatid orthobiology and the analysis of fresh blood. This implies that the person has studied at the International Academy of Somatid Orthobiology, and has been duly certified.

### D. EQUIPMENT USED

Conventional microscopic blood analysis is done using the electron microscope. During this procedure the living material must first be stained (transformed). This process does not allow the viewing of microorganisms in their natural state, nor can it be adjusted to illuminate matter through different light frequencies.

For the fresh blood analysis an ordinary compound microscope is used that has been fitted with a condenser invented by Naessens. This allows the microscope to have dark field ultramicroscopic characteristics. This means that the condenser shines an indirect light source on the specimen. This makes the specimen appear as light against a dark background. The condenser does not change the magnification or resolution of the microscope. It however enlarges the circles of diffraction around the cells and somatids. It allows the viewing of living moving blood, sharply detailed and is able to penetrate into the blood cell's interior.

### E. THE THEORETICAL BASIS OF THE FRESH BLOOD SCREENING

Gaston Naessens by the use of these unique microscopic methods has been able to find and study the somatid in live blood.

The Somatid is a motile microorganism in the blood plasma, it was first seen by Antoine Béchamps (1816-1908) in France in the mid 1800's who called them microzyma. Prof. Gu other Enderlein (1872-1968) in Germany in the early 1900's called them protids.

Naessens has found these somatids everywhere, in the sap of plants, blood of animals, in sand and even in ashes! The somatids are indestructible and are responsible for cell division. Naessens believes that the somatid is the original spark of life the pinpoint where energy condenses into matter. The somatids characteristic is that it is pleiomorphic (the original shape shifter!).

Naessens has discovered that in healthy individuals the somatids move through a three stage microcycle. When the person's body is stressed or weak then the somatid shifts into a longer macrocycle that features 13 additional stages.

Naessens claims that under certain conditions the natural gate gives way and the macrocycle emerges. When the various stages of this cycle are observed the person is at risk of developing some type of degenerative disease. It is not the somatid that is the cause of disease, it is a witness of the negative health changes occurring.

#### **F. PREPARATION FOR THE SCREENING**

Prior to participating in a fresh blood analysis the person is asked to refrain from eating food for at least four hours, and to drink plenty of water.

#### **G. THE SCREENING PROCEDURE**

The test is commenced by the extraction of one drop of peripheral blood from the finger tip. This is then placed on a slide, covered with a slide cover and sealed with oil. This permits the sample to be examined under airtight conditions.

During the first 20 minutes of analysis which the person observes on a TV screen the following may be observed.

- (a) somatids, which appear as tiny points of light moving around, as if dancing.
- (b) red blood cells or erythrocytes
- (c) white blood cells or leukocytes the three most frequently observed are:
  - (1) neutrophils
  - (2) lymphocytes
  - (3) monocytes
- (d) platelets
- (e) fibrin
- (f) components of the somatid cycle, somatids, spores, double spores, , bacterial-like forms rod-like forms, yeast-like forms, ascus-like forms and the fibrous thallus.

The analysis of fresh blood during the first 20 minutes consists of examining the following indicators:

- (a) the quantity,
- (b) the quality,
- (c) and motility ..... of the above named components.

The blood screening is considered to be negative if the above indicators are within normal ranges.

The slide of a negative screening is further observed after resting on a warm 37° C surface.

- (1) after 4-6 hours
- (2) after 24-36 hours.

During these two observation windows blood degradation is observed and analyzed. The pattern of normal blood degradation is compared with what is observed on the slide sample.

The observations consider

- (a) the rate of the blood cell degradation
- (b) the pattern of the blood cell degradation

If the above observations are not within the parameters of normal blood degradation than this indicates that the persons natural defenses are weak.

The blood degradation pattern is not a diagnostic tool it is part of the screening process.

#### **H. EVALUATION AND FEEDBACK**

The presence of the macrocycle or the presence of abnormal blood degradation patterns are indications of the weakening of the person's immune system

#### **I. OPTIONS AND CHOICES**

If the client's test is positive than various methods may be chosen to bring the person back to the microcycle.

#### **J. REPEAT SCREENING**

The greatest assets of the Naessens fresh blood analysis is that it can be used as an evaluation tool to see the effects of whatever treatment the person is using. If the persons test is positive than it is recommended to have a blood test every three months.

If a person's screening is negative than a yearly analysis is considered sufficient.

Mary KOVACS, RN, B.Sc.N.,  
(905) 562-7159  
September 13, 1998

# FUNGI

**The species specific understanding of, and difference between bacterial phase and fungal phase developments in blood pictures.**

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Diseases of the skin, digestive organs, urogenital tract, mouth, etc. are caused by the multiplication and spread of fungal microorganisms known as mycelia. Mycoses (fungal infections) range in degree from unnoticed to fatal. They are directly related to asthma and allergic rhinitis reactions. They are dealt with by the immune system and competition from other microbes or earlier developmental phases of their own cycling.

Fungal infections can be classified as:

Superficial—those that effect hair, skin, nostrils, genitals, and oral mucosa

Subcutaneous—those which occur beneath the skin

Deep—those which effect the internal organs, lungs, liver, bones, lymph, brain, heart, and urinary tract

These infections often occur in those on long-term antibiotic therapies, corticosteroids, and immunosuppressant drugs. This type of opportunistic infection is common in those with the acquired immunodeficiency syndrome, commonly known as AIDS, and also

CFIDS (chronic fatigue syndrome).

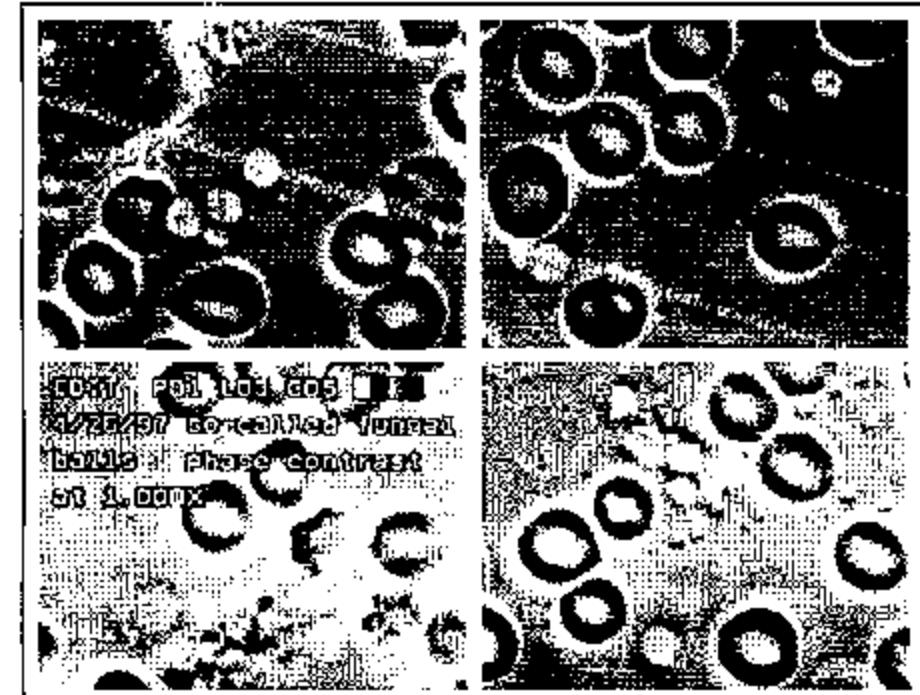
Some of these fungal forms are received from the environment, are transmitted sexually, or are transmitted through mother's milk (Candida albicans). Candida remains in non-virulent phases of development until the terrain allows for its progression into more complex pathogenic forms. The efficacy of many of the SANUM fungal remedies is based on the sexual activity of the particular species of microorganisms (and/or the benign effect altogether, through competition, on the terrain) which is initiated through the process of reinstalling the microbial flora in the body in its apathogenic earlier phases of development. The flora that was installed then copulates with the pathogenic variety and shares the sexual information of the earlier phases, which, all things being equal (terrain modulation, removal of stressors, proper diet, lifestyle, etc.) causes the pathogenic form to convert or be reduced to the apathogenic variety. It is believed that

the pathogens are also reduced in virulence through the actual activity of the copulatory process.

The main causes of pathogenic albicans overgrowth are indiscriminate antibiotic application and dental inclusions from mercury tooth amalgams. Other factors include addictions to coffee, chocolate, drugs, unsafe sexual practices, immunocompromise, stress, chemicals, radiation, improper diet, etc.

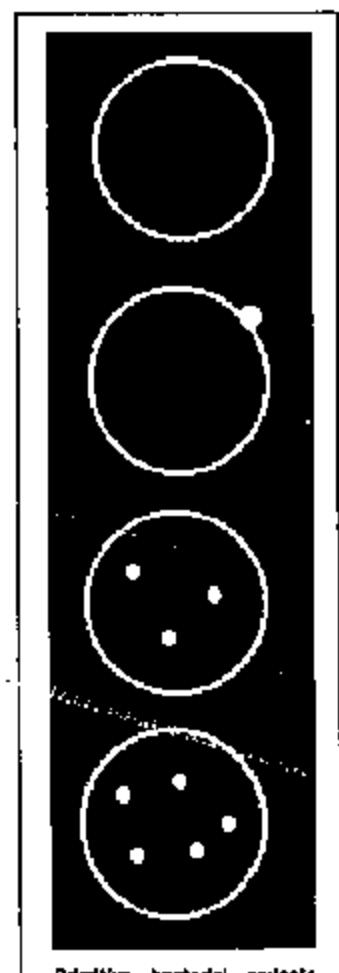
The fungal overgrowth occurs because its natural competitors have been removed, in the case of antibiotic usage. In the case of dental amalgams or metals, it is due to decreased immunity from

## Darkfield Microscopy



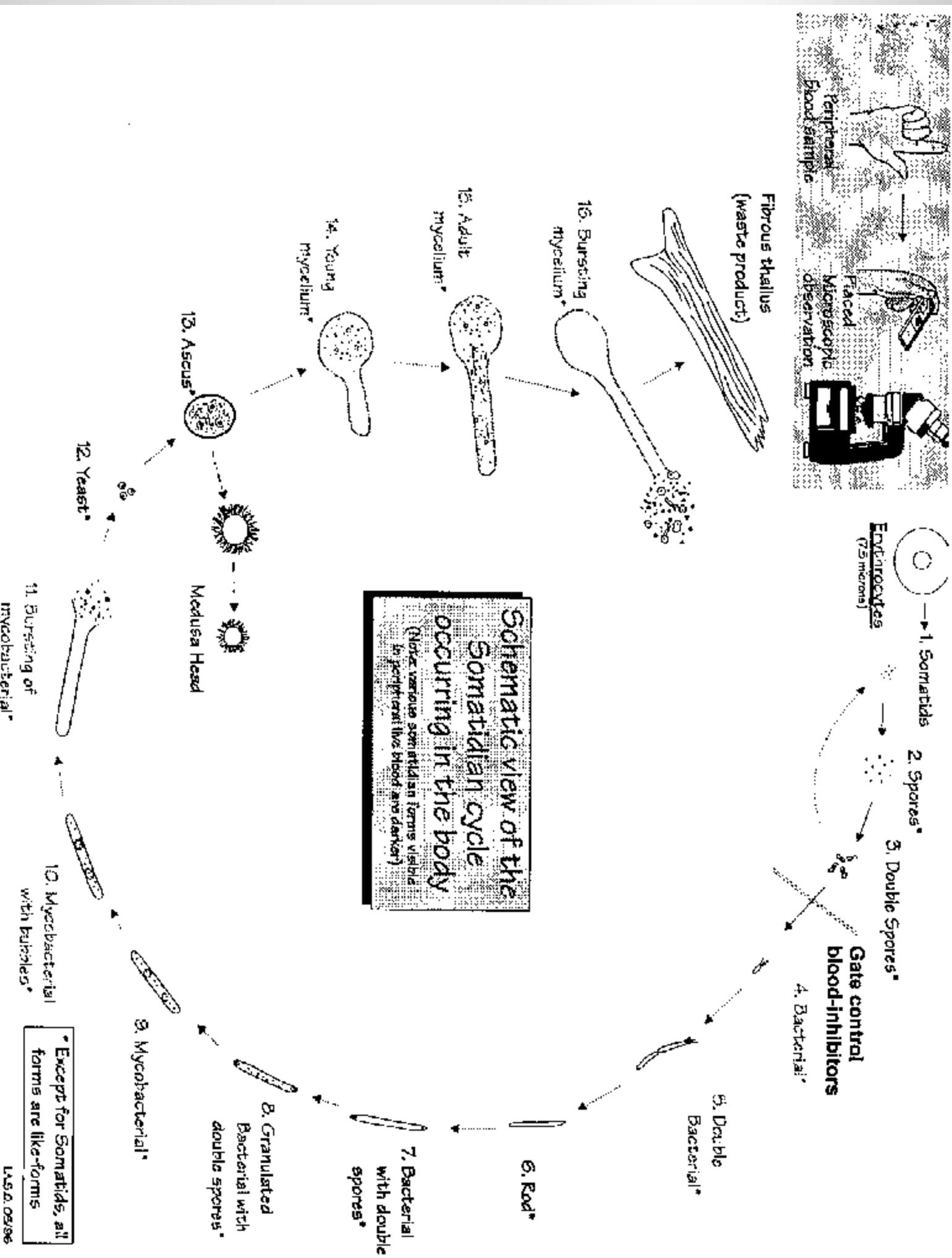
So-called fungal balls in phase contrast at 1,000X magnification. Note that the nuclei in the balls is barely or not discernable. The bacterial balls are roughly the size of the accompanying erythrocytes.

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Primitive bacterial variants (thiomycetes)

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immunocompromise. The candida also adsorbs the mercury in the gut, thereby serving the function of keeping it from moving deeper in the system, to some degree. A good inclusion in a program of remedies for alleviation of mercury toxicity in the nervous system and brain is broken cell wall chlorella, because not only is it similar to the fungus in that it adsorbs the mercury, but also carries it away.

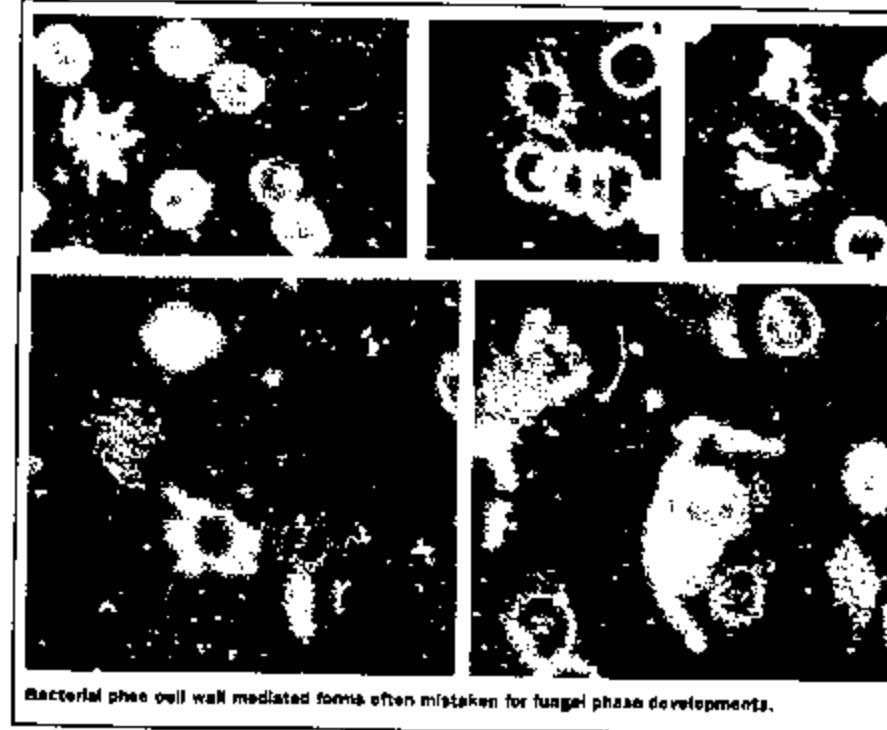
#### Primitive bacterial variants and cell wall deficient fungal species

I begin this section with a quote from "Cell Wall Deficient Forms: Stealth Pathogens" by Lida Mattman.

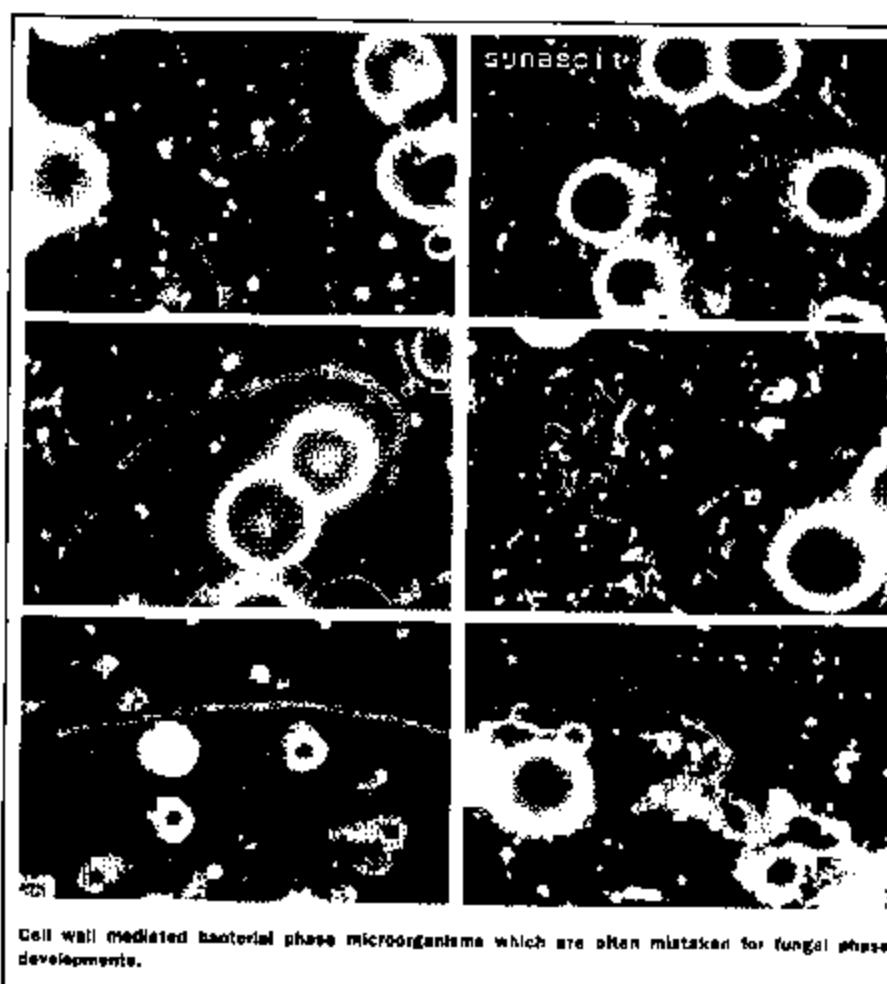
"Wall-deficient bacteria are called fungoidal as they produce yeast-like (emphasis added) budding spheres or simulate molds with elongated branching threads. (See chondrothecit and free chondrit plates, respectively). How, then, does one solve the dilemma of recognizing a wall deficient fungus? One can start with the vital activity in a fungal filtrate of *Candida Albicans* where the tiny 0.15- $\mu$ m particles cannot possibly possess the wide hard wall of the parent. Colonies developing are usually comprised of twisted Gram-negative skeins so delicate that their course is interrupted by submicroscopic gaps. These fine threads of growth have never been described as part of the classic growth of fungi. (Emphasis added where bolded)."

The above description corroborates the findings of Dr. Günther Enderlein when he described such coccoidal manifestations as being either primitive bacterial variants or the most primitive mycelian strands.

Species of microorganisms which exhibit fungal variants in tissue (in vivo) are only microscopically visible in the blood as the most elementary and minute primitive spore forms, ranging in size up from approximately 0.15 microns. The notion that anyone is viewing fungus balls in phase contrast or darkfield is technically a complete misconception, as the forms which are being regarded as fungal developments are appearing in an alkaline milieu in the blood which will not support the fungal stages of development. This is not to say that the microorganisms may not be a species that can represent fungal developments elsewhere in the body. But this species specificity is indeterminable by viewing the fresh live blood, as there is not a way to distinguish which species is being viewed without culturing it out through the use of a medium, or by aging or heating the sample, under some condi-



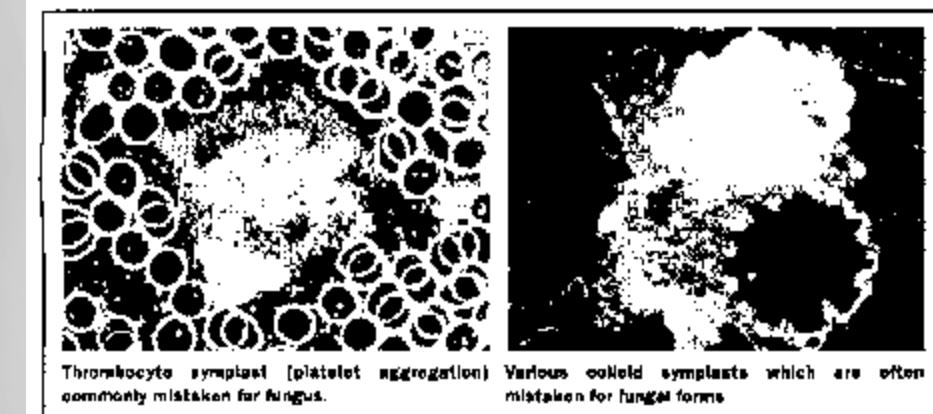
Bacterial phase cell wall mediated forms often mistaken for fungal phase developments.



Cell wall mediated bacterial phase microorganisms which are often mistaken for fungal phase developments.

tions. This process changes the phase of development into phases that do not appear, again, in the alkaline milieu of the

blood. The forms that are being viewed (and mistaken for fungus stage) are actually colloid thecits, thrombocytes, chon-



Thrombocyte symbiots (platelet aggregation). Various coccoid symbiots which are often mistaken for fungal forms.

drits, ascirs, synascirs, and mychirs, all of which are part of the bacterial phase of development, which develops in an alkaline milieu. Also, the cell wall deficient forms, chondrits which are symbiots, are mistaken for fungal appearances. These chondrits do represent a fermentative process, but not at the level of a fungal appearance. They are even an earlier stage appearance than the most primitive cell wall mediated bacterial variants. The species, again, are unspecified upon appearance, as they are the same common stages that appear in many species of microorganism developmental cycles.

Some of these developments in polymorphic progressions are actually thrombocytes, and act as regulators, per Dr. Enderlein, and even (in some species) emerge from the red corpuscles in the serum. Some of these ball or balloon-like forms may become functionally pathogenic under certain specific terrain related conditions, and conversely, some of these developments certainly are an expression of the body's capacity to mount a defense. The possibility of making these determinations within this phase of bacterial cellular developments requires that the viewer be able to distinguish the number of nuclei which appear within these delicate diaphanous bacterial cells. This microscopic imagery is only obtainable in a true, ultra illumination darkfield, employing superior plan achro or plan apo medical grade oil immersion iris diaphragm objectives and the proper condenser, which would be of the oil immersion variety also. This determination of the developmental progression of the bacterial variants is generally not able to be made in a phase contrast or differential interference field microscopically, because these fields generally do not provide adequate resolution to count the nuclei which appear within the ball-like cells that develop in conjunction with their primary nuclei (which

are the cell wall deficient symbiots until they develop this cell wall mediated appearance). This is a crucial determination which must necessarily be made in order to distinguish the function which is related to the cell's very appearance. It should also be noted that the pathogenicity of most microbes only exists in one stage of development, being either viral sized, bacterial or fungal. The exception to this is the Endobiont, *Mucor racemosus* Freien, wherein any stage above the primitive stages is pathogenic.

Candida is never observed in its fungal phase in the blood because the blood's inherent alkalinity supports its development only to a spore stage. These spores are extremely minute, and do not progress to visibility at the level where they can be distinguished from other similar microorganisms in the blood except possible through staining. The primitive bacterial phase microorganisms that are mistakenly called fungus may be part of the developmental phase of a species that has a fungal variant or may culminate as a fungus, but it is an error to call it a fungus in the blood. It is a species that has a fungal variant, and may also have a bacterial phase that occurs in the alkaline milieu of the blood. The ball-like appearances are bacterial phase developments.

These so-called 'fungal balls' appear very similar to each other, regardless of the number of nuclei, in phase contrast, but differ greatly in the higher resolution of Ultra darkfield. In the Ultra-darkfield the number and valence of the nuclei determines their status as potential regulators or pathogens, and it is a mistake to classify them all as the same thing, or as having the same function. Therefore, there may be a thecit (primitive bacterial) phase in the life cycle of the species *Candida Albicans*. It follows that if *Candida* appears in the blood, it



Electron scanning micrograph of Chondrits emerging from erys. From Baker, R.F., J. Ultrastruct. Res., 11, 494-507, 1964.



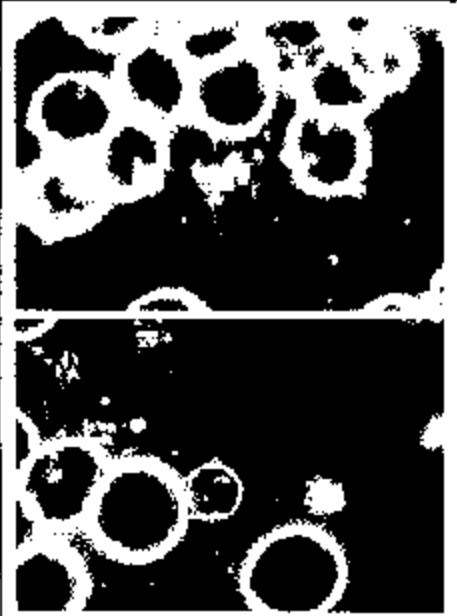
Free chondrits (coccoidal phase bacterial variants) at 500x

may exhibit a bacterial phase rather than the fungal phase, or certainly will appear as cell wall deficient spores.

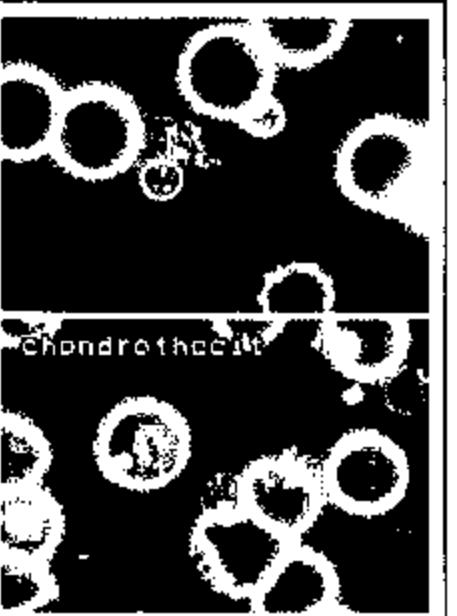
Virus is a primitive stage of development of all microorganisms share and this phase is virtually invisible in the present context of known light microscopy techniques. Microbes are ubiquitous and can rise to their pathogenic phase from any other phase, as their progression is not linear, and the progression is terrain dependent. One must know which stage is pathogenic in order to treat related conditions. For instance, acid-fast rods are not necessary for tuberculosis.

#### *Candida Albicans*

This may be one of the most controversial and misunderstood areas in natural



Highly visible nuclei in primitive bacterial thecites as viewed in ultra-darkfield at 1,000X. Note that the nuclei are very visible, allowing for evaluative differentiation of function of the microorganisms. These are the same microorganisms as viewed in the phase contrast pictures above.



chenaretheccit

can be considered to be a third primary potential parasite, along with *Mucor* and *Aspergillus*, because of the advent of runaway antibiotic usage over the many years. The only difference is that there is no known symbiosis occurring from the presence of *Candida Albicans* in the body.

Certain vegetable species colloidal microorganisms produce particular acids to maintain their environment. Examples of this are:

- *Mucor*—lactic acid
  - *Aspergillus*—citric acid
  - *Penicillium*—penicillic acid

The developmental life-cycle of microbes require differing pH conditions. Some microorganism species find their culminating phase of development in the bacterial phase. The different phases of development of microorganisms require the following terrains for development:

- virus, microbe, or primitive form—strongly alkaline
  - bacterial phase—weakly alkaline
  - fungal phase—acidic

This developmental process is related to leaky gut syndrome, as the tissues are weakened, even by the infection. The microorganisms continue to multiply and then invaginate the venous wall (in spore form) and are carried again out of the bloodstream and multiply in the tissues where they deposit their acids, thereby enhancing the acid pH which they require for propagation. This is why individuals with candida feel acidic. At this point in the total progression of the problem, it is not just because their diet is acidifying. An acidifying diet may be one of the original factors which contributed to this complex problem, though. At this stage it probably will not be possible to balance the pH through diet alone, because of the proliferation which is creating and maintaining its own environ-

creating and maintaining its own environment, at that point, through the processes inherent to its upward development which are related to the production of acids. To achieve the necessary optimum pH balances, these individuals must use some combinations of Alkali (or other bicarbonate combinations), baking soda baths, lemon juice and maple syrup combination (juices only where tolerated), fresh pineapple juice, and electrolyte solutions such as Cell Food, macro minerals, and all citrus fruits and their juices (again, if tolerated). At this point the reader may think "Fruit juices are full of yeast and sugars. Doesn't this feed the yeast?". This is true, but the point should not be to try to create a dietary approach

ed), fresh pineapple juice, and electrolyte solutions such as Cell Food, macro minerals, and all citrus fruits and their juices (again, if tolerated). At this point the reader may think "Fruit juices are full of yeast and sugars. Doesn't this feed the yeast?". This is true, but the point should not be to try to create a dietary approach



Scanning electron photomicrograph of *Candida Albican*. Courtesy of SANUM Kahlbeck.



### **Chondratmecits or primitive bacterial phase microorganisms**

remedies (isopathic combinations), ozone, colloidal silver, Beck's box, and Rife type or other electromagnetic field generators. These therapies may be effective in numerous different ways and for varying reasons and must be recommended and guided by an experienced practitioner who will know how to combine all of the different elements. Often individuals expect immediate, symptomatic relief. In reality, one should expect to feel worse first, as a great deal of eliminative activity is in order. So it is important to understand that this condition was not created in all of its severity overnight, and it may take a fair amount of time in order to reestablish balance. For severe fungal infections a good approach is to utilize Utilin, Latensin, Pe-frakehl, Notskehl, and Albicansan, w/ Alkala, colon cleansing, and kidney and liver drainage. Again, the stressors must be removed first or simultaneously.

The SANUM remedies reintroduce the original form of the microbe which appears in the body and is harmless, before it mutated. In a regulated pH environment this benign form copulates (exchanges information) with the pathogenic forms and they devolve into their original apathogenic forms and can be maintained in that range of development.

The mode d'employ of Rife generators is to disturb the microbe's progression through the application of electrical Herzian fields and also through the stimulation of interleukin II and other immune factors.

in order to cope forever with the problem, but rather to just create a diet which is tolerable and supportive to elimination and then to deal with the problem therapeutically with other means being the primary methods. The imbalancet is not created strictly by dietary imbalances and is not eliminated in this fashion either. I will elaborate to some degree on these approaches further on in the article.

pH balancing and gut flora enhancement or replacement alone will not affect this condition, and most practitioners experience temporary results or failure if they attempt this in combination with an exclusively dietary approach. Most will find some relief with this approach (diet combined with flora replacement) but will then end up living off of the shelves of health food stores, on a continual supplementation regimen that addresses some percentage of the associ-

and have some percentage of the associated symptomatology and pathology. The reason for this failure is that the candida has the upper hand in the gut and also systemically, and has to be weeded out first or simultaneously, through utilization of therapies that the yeast cannot mutate around (as in the case of Nystatin and other antifungals).

These therapies may include SANUM

Colloidal silver interferes with the enzyme system that the anaerobic microbes use for respiration. Therefore they cannot mutate around it or become resistant and are eliminated instead. Special care must be taken with colloidal silver to use one that is strong enough and simultaneously supplement the gut flora, as the silver can also interfere with aerobic microorganisms. Failing to supplement the flora, or using a product that only contains 3 to 5 parts per million of silver, appears to be the main limitations in terms of effectiveness. Naturally this approach, like any other, must be accompanied by a full regimen that includes cycles of purification, balancing, and rejuvenation. Contrary to popular gossip to the contrary by invested promoters, there appears to be some negative side effects to colloidal silver consumption, when used over long periods of time and in relatively high amounts. These include drainage problems and the destruction of intestinal floras. For some, the results of oral use have been complicated gastro intestinal dysbioses and Fortakelh, Albicans and Pefrakehl and other SANUM preparations in combination may be a better approach as they do not tend to produce those negative results.

Many individuals have been known to exhibit extreme Hersheimer's (healing crisis) reactions with silver. This has particularly been a problem with chronic fatigue syndrome. Lymphatic drainage (homeopathic, herbal, or 714-X, which also regulates the immune system) along with juicing, consumption of a minimum of eight 8 oz. glasses of Crystal Energy water and/or other natural fluids such as juices and herbal teas, colonics or colemas, lymphatic massage, dry brush massage, bouncing exercises, and walking are all required in combination with colloidal silver and also the other aforementioned approaches. It is not useful or necessary to load up the body with unnatural numbers of metals such as silver over extended periods of time in order to maintain good health. It is better to understand the overall biological terrain requirements and meet them through the adjustment of lifestyle. Nevertheless, it may be very useful to apply colloidal silver for a measured period of time because of its ability to interfere with the respiratory enzymes of the microorganism. They also cannot mutate around this effect.

Ozone will cause less of a negative reaction than silver. The reaction will not as likely be a result of the breakdown



Ascus emerging from yeast



Bacterial phase ascus

of toxins, but rather congestion in the lymph and liver. This is because the ozone reduces toxins to ash, so they don't get recycled through your bloodstream as poisons on the way out (and by association, through the brain). The Rife and Beck therapies also require all of the same drainage requirements, and the lymphatic shunt (Beck's design) may be useful while the fungus is being reduced. The best approach, as always, is to combine elements based on the individual's tolerance and needs. Diet alone most likely will not correct this condition of candida overgrowth, but is certainly a necessary adjunct to any program. The dietary needs and reactions will be observed to change greatly after the problem has been addressed.

Many people have been misled through the wrongly held beliefs of most primarily dietarily oriented natural therapists on this subject. Therefore, I recommend that practitioners understand that the microbe must be reduced both in number and also to its apathogenic form, while adjusting the pH. Acidophilus replacement is not the answer, as the higher phase dominant yeast forms (which have overwhelmed the immune system's capacity to control them) are at such a high valence that they just feast on or suppress the installed lactobacillus strains when the subject is without proper therapeutic intervention. This mycotic condition was not generally created through dietary means alone, and although diet will be extremely necessary and instrumental in a program of complete recovery, it will not on its own be adequate therapeutically, which is the overwhelming and ongoing experience of the numerous masses who are led in

the direction of this belief. The human response is to overwhelmed and the body temporarily adds a "second immune system" in the form of the aforementioned therapeutic approaches, or other effective means.

All of the aforementioned therapeutic approaches (excepting Fungi Specific, for some) also relate to how to deal with Chronic Fungal Syndrome, although there are also many other factors (especially toxicological) which need to be dealt with. See "The Ten Underlying Causes of Illness and What to Do About Them" by Michael Coyle, for a more complete explanation regarding these syndromes.

It may or may not be necessary for the client to eliminate all yeast-containing products (breads, dairy products, yeast related supplements), from the diet. The elimination of these foods is only necessary if they are reactive to them. There is no sound basis in the notion that yeast, yeast or brewer's yeast, feeds fungus. Yet again, this when fungal conditions can be exacerbated by anything, including yeast containing foods and food supplements. Insects are also an extreme deterrent to yeast.

Since microorganisms compete for terrain in the body, it is necessary and useful corrective approach to supplement body floras once the problem has been identified. The gut should contain a sufficient of beneficial microorganisms, and measurable in pounds. Flora replacement is therapeutic in that the flora will compete with anaerobic microorganisms and thereby reduce their number, especially once therapeutic intervention has reduced the valence of the candida. This is why aerobic microorganisms are encouraged to be the dominant part of the immune system, which should be present at least 65%, and optimally 100% of the flora existing in the gut.

An oral flora for gut flora supplement should be used during a program of correction of mycotic dysbiosis, is any so called "yeast" which contains:

- L. acidophilus
- B. longum
- L. planatarum
- L. ruteri
- L. salivarius
- L. bulgaricus
- E. faecium
- S. thermophilus
- Fructo Oligo-Saccharides
- Calcium, zinc, etc.
- Trace elements
- Alkaline and alkaline minerals

for fungus, and Notakehl and Okubasan for reestablishing gut flora. The water drawn off of hulled barley, drunk, is also useful in reestablishing flora. Use one part barley to one part water, leave it overnight, and drink freely.

Many fungal disorders respond well to a series of courses of Latensin, Notakehl, Pefrakchl, Fortakehl and Albi-cansan. Reactions may accompany these remedies, and they should only be administered by a trained health professional. These remedies are not antibiotic, but pro-biotic, and work remarkably well. Because the type of fungal dysbiosis which is occurring will not be determinable in the blood picture, the remedies must be applied on the basis other forms of testing such as point testing, Kinesiology, etc.

A strong empirical understanding of how the condition presents and what the primary stressors are in the subjects total life picture is likely the most important means of evaluation of both condition and remedy. \*

#### ABOUT THE AUTHOR

Michael Coyle is a Natural Therapist, researcher and educator, and the author of the definitive "NuLife Sciences Applied Microscopy for Nutritional Evaluation and Correction" Workbook text. Michael generally conducts monthly or bimonthly training for health care practitioners in live blood analysis. For further information on NuLife Sciences and Michael's work and for a schedule of training dates and a complementary microscopy equipment catalogue, please see below. Also you may search under NuLife Sciences on the worldwide web for further information.

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## Shark Senses

Mary Ann Badavi & Stephanie Parker



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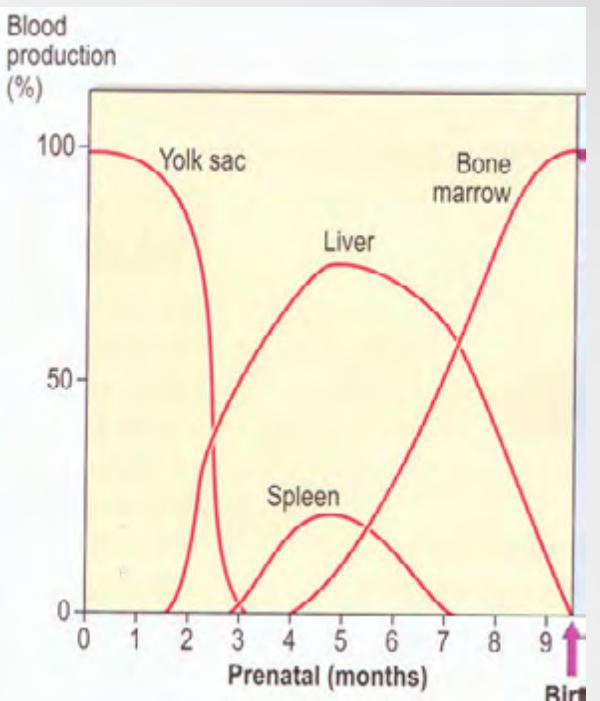
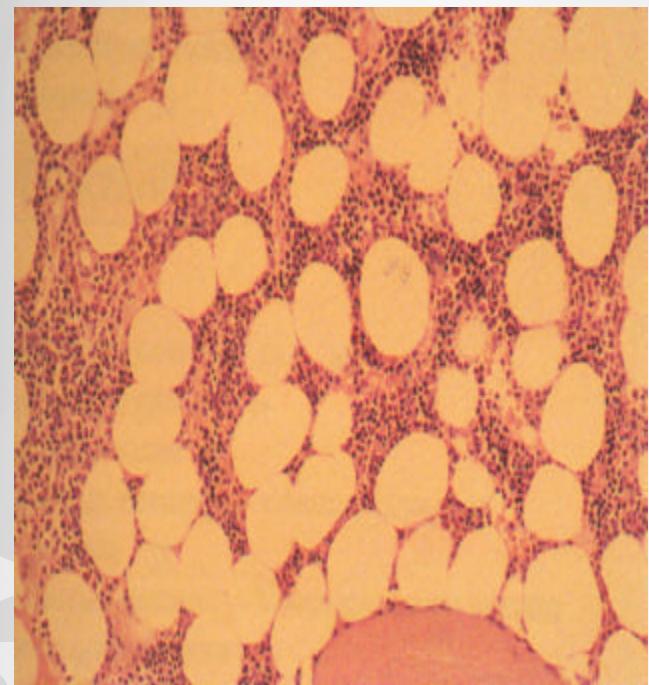
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- The bonnethead shark has an electrosense that is five million times greater than the electrosense of humans.

Picture: Andy Murch/Elasmidiver.com

- It is also thought that the Hammerhead shark evolved its head to increase surface area for electrical reception.

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## THE BONE MARROW

In early fetal life, blood is produced in the mesoderm of the yolk sac. During the second to seventh months the liver and spleen take over. Only in the last 2 months of fetal development does the bone marrow become the predominant site of blood formation. During childhood, marrow in the more peripheral bones becomes gradually replaced by fat, so that in adult life over 70% is located in the pelvis, vertebrae and sternum (Fig. 1). This explains the sites used for bone marrow sampling.

Fig. 1 Sites of blood production in the fetus and after birth.

### THE STRUCTURE OF THE BONE MARROW

A trephine biopsy allows a two-dimensional view of the bone marrow down the light microscope (Fig. 2). Haematopoietic cells of varying lineage and maturity are packed between fat spaces and bony trabeculae. Ultra-structural studies reveal clusters of haematopoietic cells surrounding vascular sinuses which allow eventual discharge of mature cells into the blood. Different lineages are compartmentalised; for example, the most immature myeloid precursors lie deep in the marrow parenchyma whilst more mature forms migrate towards the sinus wall. Lymphocytes tend to surround small radial arteries whilst erythrocytes form islands around the sinus walls. Blood precursor cells in the marrow exist in close proximity to stromal cells. Stromal cells are those cells which do not mature into the three main types of peripheral blood cells thus they include macrophages, fat cells, endothelial cells and reticulum cells.

Immature blood cells are attached to these stromal cells by multiple cellular adhesion molecules (e.g. fibronectin and collagen). Adhesive molecules have specific receptors on stromal and haematopoietic cells. As blood cells mature, the receptors down-regulate and the cells become less adherent and commence the journey through the sinus wall and into the blood stream. The regulation of receptors is under the control of growth factors described below.

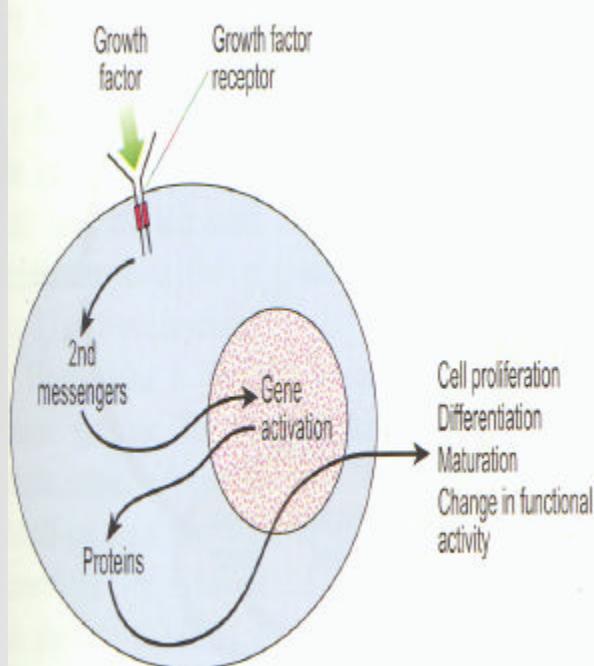
Fig. 2 Normal bone marrow

### HAEMATOPOIESIS: THE STEM CELL HIERARCHY

Haematopoiesis means the formation of blood. The punctual release of blood cells from the marrow described above is the culminating event in a process simple in concept but complex in terminology. Figures show how the cells recognisable in blood are ultimately all derived from pluripotential stem cells. Stem cells are not detectable by microscopic techniques but their existence can be inferred from cell cultures. Culture of these early cells on agar generates groups of more mature and thus recognisable progenitor cells known as colony forming units (CFUs). For myeloid development the earliest detectable precursor cell creates granulocytes, erythrocytes, monocytes and megakaryocytes and is thus called CFUGEMM. If we focus on neutrophil development it can be seen that CFUGEMM engenders the more committed precursor cells CFUGM and CFUG prior to the development of the myeloblast, the first cell in the sequence to be recognisable by light microscopy. Pluripotential cells have the capacity for self-renewal as well as differentiation and the system allows enormous amplification. A lifetime of human haematopoiesis with the generation of incalculable numbers of mature cells may rely on only a few thousand stem cells present at birth.

### GROWTH FACTORS

The events described above require regulation. This control is mediated via a group of haematopoietic growth factors. Growth factors are generally glycoproteins produced by stroma and differentiated blood cells. They may act on more than one cell lineage and frequently show additive and synergistic interactions with each other. Their actions are multiple, including the promotion of proliferation, differentiation and maturation, as well as changing

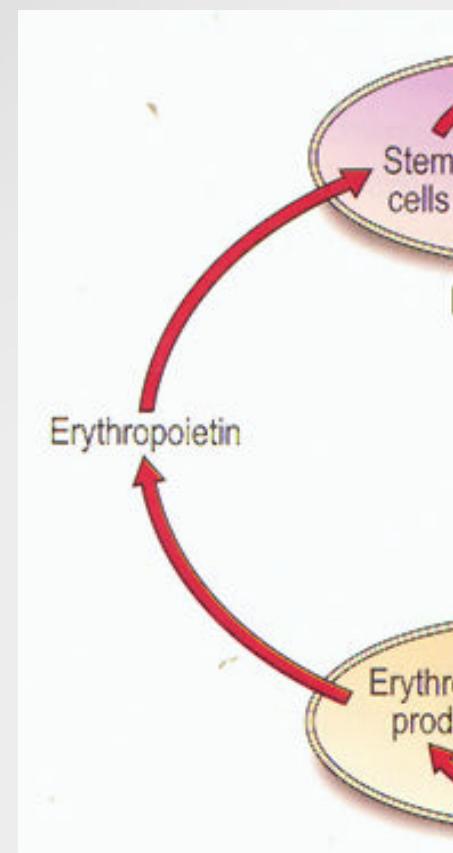


functional activity. Growth factors alter the behaviour of cells by interacting with specific receptors on the cell surface (Fig. 3). Receptors for several growth and differentiation factors have been molecularly cloned and shown to be related in structure (the 'haematopoietic growth receptor family'). The combination of factor and membrane receptor leads to a structural change in the receptor and the triggering of a complex sequence of biochemical events (signal transduction). Activation of tyrosine kinase domains in the intracellular part of the receptor is a common mechanism (e.g. receptors for M-CSF and c-kit ligand), but there are others. The end result is the generation of intracellular regulators in the cell cytoplasm (e.g. protein kinase C, calcium ions) which have the capacity to activate genes, which in turn encode proteins essential in cell activation. Receptors are themselves highly regulated with changing numbers during cell differentiation and modulation by their own and other growth factors. Several growth factors have common receptor sub-units and mechanisms for signalling. Under normal circumstances growth factors circulate in the plasma at virtually unidentifiable levels. The activities of many factors are likely to be localised and transient so that systemic levels are of limited significance. For instance, in the marrow, factors acting at the earliest stages of haematopoiesis (e.g. c-kit ligand) are released from stromal cells in close proximity to haematopoietic precursor cells. Major haematopoietic growth factors and their key actions are illustrated. Again, the nomenclature is confusing. The colony stimulating factors (CSFs) were originally defined by their ability to stimulate blood progenitor cells while the interleukins (ILs) were defined by their effects on mature lymphocytes. Subsequent discoveries have rendered this dual nomenclature unhelpful - thus IL-3 is a key stem cell growth factor and is more logically grouped with the CSFs. The term cytokine incorporates all growth factors.

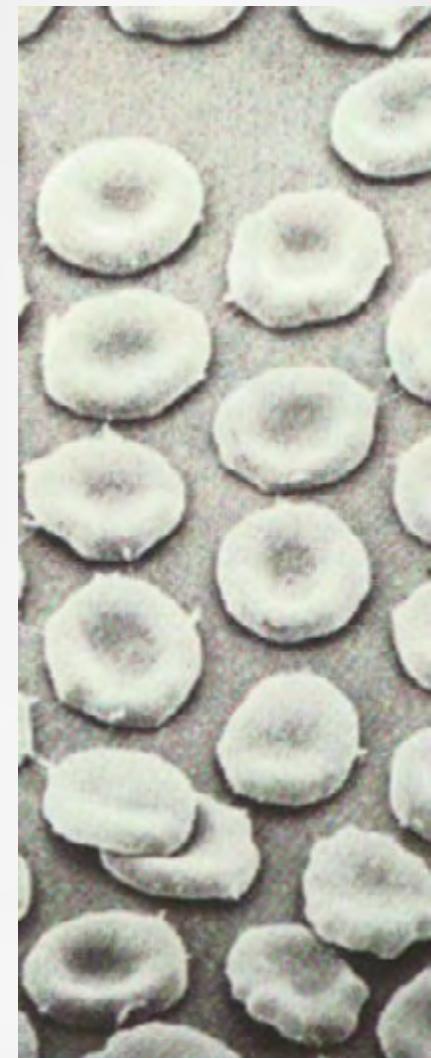
Fig. 3 Schematic view of action of growth factor on haematopoietic cell.

### The bone marrow

The bone marrow is the site of blood formation (haematopoiesis) after birth. The cells recognisable in the blood are ultimately all derived from pluripotential stem cells in the marrow. Immature blood cells in the marrow are attached to stromal cells by multiple cellular adhesion molecules. Maturing blood cells are eventually released through vascular sinus walls into the blood stream. Regulation of haematopoiesis is mediated via a group of haematopoietic growth factors - these interact with specific receptors on the surface of haematopoietic cells.



## RED CELLS



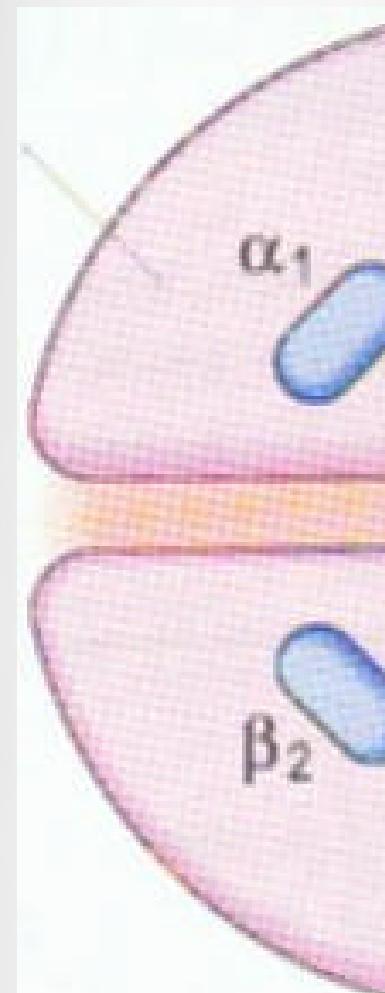
The mature red cells of the blood transport the respiratory gases, oxygen and carbon dioxide ( $\text{CO}_2$ ). Oxygen is carried from the lungs to the tissues where it is exchanged for  $\text{CO}_2$ . Red cells are equipped to perform this function for 120 days during which they make a 300 mile journey around the microcirculation. Prior to discharge from marrow sinuses into the peripheral blood, red cells shed their nuclei. This gives the advantages of reduced weight and transformation into a biconcave disc with increased deformability compared with the more rigid spheroidal nucleated precursor (Fig. 1). The blood volume is comprised of the mass of red cells and the plasma. Plasma volume is regulated by stretch receptors in the heart and kidney which influence secretion of antidiuretic hormone (ADH) and aldosterone. Erythropoiesis is regulated chiefly by the growth factor erythropoietin.

**Fig. 1** Scanning electron microscope picture of mature red cells showing clearly the characteristic biconcave shape,

### ERYTHROPOIETIN

Unlike other growth factors, erythropoietin is mainly synthesised by the peritubular endothelial cells of the kidney. Production is triggered by tissue hypoxia (lack of oxygen), although the precise mechanism is unclear. Erythropoietin molecules bind to specific membrane receptors on primitive erythroid cells in the bone marrow and induce maturation. The increase in red cells released into the blood stops when normal oxygen transport is restored - this feedback circuit is illustrated in Figure 2.

**Fig. 2** Feedback circuit in production of erythropoietin.



### STRUCTURE

The mature red cell is around  $7.8 \mu\text{m}$  across and  $1.7 \mu\text{m}$  thick. Its biconcave shape allows maximum flexibility and an umbrella shape is adopted to traverse the smallest capillaries which have diameters of only  $5 \mu\text{m}$ . The ability of red cells to recover from the recurrent stresses of the turbulent circulation hinges on the design of the membrane.

The red cell membrane is composed of a collapsible lattice of specialised proteins (the 'cytoskeleton') and an outer lipid bilayer (Fig. 3). The protein skeleton is responsible for maintaining red cell shape whilst the lipid bilayer provides a hydrophobic skin. The four skeletal proteins are spectrin, actin, protein 4.1 and ankyrin. Spectrin is the most abundant and consists of alpha and beta chains wound around each other. Spectrin heterodimers can align at the ends to form tetramers (i.e. four chains). Spectrin tetramers are joined together by actin in association with protein 4.1. This flexible skeleton is attached to the rest of the membrane by ankyrin which links the spectrin beta chain to the cytoplasmic end of the transmembrane protein Band 3. The lipid bilayer consists mainly of a mixture of phospholipids and cholesterol. Cholesterol molecules are inserted between phospholipid molecules in such a way that they stiffen the membrane whilst still allowing a degree of fluidity between the bilayers.

Defects of both the red cell membrane proteins and lipids may lead to changes in red cell shape and premature destruction.

### METABOLISM

Red cells require an energy source to maintain their structure and also a mechanism for detoxification of oxidants. Energy is provided by the *Embden-Meyerhof pathway*, a sequence of biochemical reactions in which glucose is metabolised to lactate with the generation of two molecules of ATP. ATP maintains the osmotic pressure of the cell by driving sodium

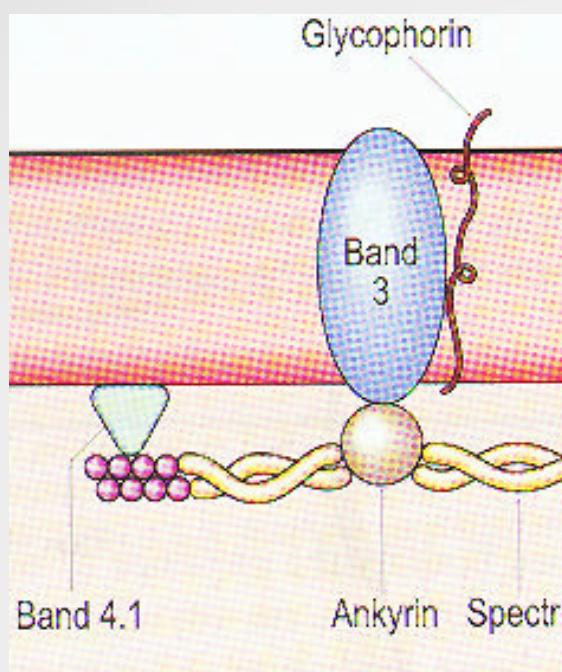
and calcium pumps in the membrane. It also provides energy for the cytoskeletal changes needed for recovery of cell shape. The Embden-Meyerhof pathway does not require oxygen as a substrate but a small amount of oxidative glycolysis occurs by the *hexose monophosphate shunt* in which glucose-6-phosphate is metabolised to generate NADPH. The hexose monophosphate shunt plays a vital role in oxygen detoxification and when oxidised substrates accumulate in the cell it increases activity several fold. Inherited deficiencies of red cell enzymes in either the Embden-Meyerhof pathway (e.g. pyruvate kinase) or the hexose monophosphate shunt (e.g. glucose-6-phosphate dehydrogenase) can lead to shortened red cell survival and haemolytic anaemia.

### HAEMOGLOBIN AND OXYGEN TRANSPORT

**Fig. 3** The essential elements of the haemoglobin molecule.

The key function of red cells, to carry oxygen to the tissues and return  $\text{CO}_2$  from the tissues to the lungs, depends on the specialised protein haemoglobin which is present in large amounts in mature cells. The normal adult haemoglobin molecule ( $\text{HbA}$ ) contains four polypeptide chains ('globin' chains): the two alpha chains and two beta chains are often notated as  $\alpha_2\beta_2$ . Combined with each of the polypeptide chains is a 'haem' molecule which contains ferrous iron ( $\text{Fe}^{2+}$ ) and protoporphyrin (Fig. 3). The iron combines reversibly with oxygen and thus haem forms the oxygen carrying part of the molecule. Other globin chains are formed by the fetus and the change from fetal to adult haemoglobin occurs in the first 3 to 6 months of life. However the subunits designated  $\gamma$  and  $\delta$  persist into later life and small amounts of fetal haemoglobin ( $\text{HbF}$ ;  $\alpha_2\gamma_2$ ) and  $\text{HbA}_2$  ( $\alpha_2\delta_2$ ) are found in adults.

Haemoglobin is more than an inert carrier molecule. The individual globin chains interact with each other to facilitate the off-loading of oxygen at lower oxygen saturations. The metabolite 2,3-Diphosphoglyceride (2,3-DPG) generated in a side-arm of the Embden-Meyerhof pathway has an important role in the process which results in a sigmoid shaped oxygen dissociation curve. In anatomical terms haemoglobin has a high affinity for oxygen in the



lungs and a much lower affinity in the tissues. The oxygen dissociation curve moves to the left when oxygen affinity increases; this occurs when  $\text{H}^+$  ion concentration is reduced or haemoglobin F (which cannot bind 2,3-DPG) raised. The curve moves to the right when oxygen affinity decreases; for instance when 2,3-DPG concentration rises or the abnormal sickle haemoglobin (HbS) is present. The  $P_{50}$  level is defined as the partial pressure of oxygen at which haemoglobin is half saturated.

#### AGEING AND DEATH

Beyond 100 days red cells start to show features of ageing including a declining rate of glycolysis, reduced levels of ATP and membrane lipid, and a loss of flexibility. The terminal event is unclear but effete cells are removed from the circulation by the macrophages of the liver and spleen. Most of the catabolised haemoglobin, particularly the iron, is reused. The protoporphyrin of haem is metabolised to the yellow pigment bilirubin which is bound to albumin in the plasma. Bilirubin is conjugated in the liver to a water soluble diglucuronide that is converted to stercobilin and stercobilinogen and excreted in the faeces. Some stercobilin and stercobilinogen are reabsorbed from the intestine and excreted in the urine as urobilin and urobilinogen.

Fig. 4 The red cell membrane.

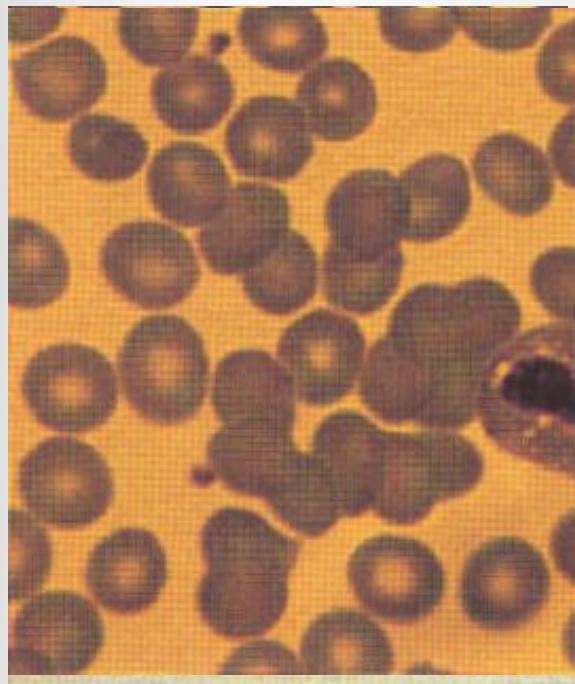
#### Red cells

Erythropoiesis (the formation of red cells) is regulated by the growth factor erythropoietin. Mature red cells have a biconcave disc shape and no nucleus.

The red cell membrane consists of a lattice of specialised proteins and an outer lipid bilayer. Red cells derive energy principally from the metabolism of glucose to lactate (Embden-Meyerhof pathway).

Red cells contain a specialised protein, haemoglobin, which allows carriage of oxygen to the tissue and return of  $\text{CO}_2$  from the tissues to the lungs.

Beyond 100 days red cells start to show features of ageing including a declining rate of glycolysis, reduced levels of ATP and membrane lipid, and a loss of flexibility. The terminal event is unclear but effete cells are removed from the circulation by the macrophages of the liver and spleen. Most of the catabolised haemoglobin, particularly the iron, is reused. The protoporphyrin of haem is metabolised to the yellow pigment bilirubin which is bound to albumin in the plasma. Bilirubin is conjugated in the liver to a water soluble diglucuronide that is converted to stercobilin and stercobilinogen and excreted in the faeces. Some stercobilin and stercobilinogen are reabsorbed from the intestine and excreted in the urine as urobilin and urobilinogen.



## NEUTROPHILS, EOSINOPHILS, BASOPHILS AND MONOCYTES

The term 'white cells' or 'leucocytes' refers to the nucleated cells of the blood - the neutrophils, lymphocytes, monocytes, eosinophils and basophils. All these cells play a role in defending the host against infection and other insults. Neutrophils, monocytes, eosinophils and basophils are phagocytes. They engulf and destroy foreign material and damaged cells. The term 'granulocytes' may be used to particularly describe neutrophils, eosinophils and basophils.

### NEUTROPHILS

The blood neutrophil (Fig. 1a) is the end-product of an orchestrated sequence of differentiation in the myeloid cells of the bone marrow. The mature cell has a multi-lobed nucleus and small granules ('secondary' or 'specific') in the cytoplasm. Neutrophils have a limited lifespan of around 10 hours in the blood. Approximately half the cells are included in a normal blood count (the circulating pool) the remainder being in the, 'marginal pool'. The essential function of all these cells is to enter the tissues and combat infection. This requires both migration to the site of infection or tissue injury (chemotaxis) and the destruction of foreign material (phagocytosis). Normal chemotaxis is dependent on the release of chemotactic factors generated by bacteria and leucocytes already present at the infection site. Such factors provide the stimulus for neutrophils to leave the circulation and enter the extravascular space.

Neutrophil mobility is imbued both by the presence of adhesion molecules on the cell surface and an actin-myosin assembly in the cell membrane, the latter mediating the movement necessary for locomotion and phagocytosis.

Once the cell is at the target site the foreign antigen or particle is engulfed within a phagocytic vacuole. There are various methods of killing; key mechanisms are reduction of pH within the vacuole, the release of digestive enzymes and oxidative metabolism in which antimicrobial oxidants are formed (the 'respiratory burst'). Cytokines such as G-CSF and GM-CSF not only increase neutrophil production but also promote chemotaxis and phagocytosis.

In clinical practice an increase in neutrophils in the blood ('neutrophil leucocytosis' or 'neutrophilia') is a common accompaniment to infection and tissue injury (Table 1). The strain on the neutrophil compartment often leads to younger 'band forms' being discharged from the marrow into the blood stream and the appearance of toxic changes, including coarsened granulation and vacuolation. Occasionally, phagocytosed bacteria are visible.

Reduced neutrophils in the blood (neutropenia) is seen in a wide range of inherited and acquired disorders. Serious infection is not seen regularly until the count falls below  $0.5 \times 10^9/\text{l}$ . Neutropenia may be an isolated abnormality or associated with a pancytopenia. Some common causes of an isolated neutropenia are listed in Table 2. In general, neutropenia may be caused by underproduction from the marrow (e.g. leukaemia), reduced neutrophil lifespan (e.g. immune neutropenia), or pooling of neutrophils in a large spleen. It is important to remember that drugs may be responsible. The term *benign idiopathic neutropenia* is used to describe a moderate neutropenia caused by an increased fraction of cells in the marginal pool with a resultant reduction in the circulating pool. The disorder is familial and is not associated with an increased risk of infection. A similar mechanism explains the lower neutrophil normal reference range in black people compared with that in white people. In the genetic disorder, *cyclical neutropenia*, the neutrophil count falls every 14-21 days and recurrent infections occur.

In addition to quantitative abnormalities, neutrophils can be functionally abnormal. There are several rare inherited diseases characterised by impaired neutrophil adherence, chemotaxis or bactericidal activity. In *chronic granulomatous disease*, neutrophils are able to phagocytose but not kill catalase-positive microorganisms. Inheritance is autosomal or X-linked and patients suffer recurrent purulent infections and associated granuloma formation. Diagnosis is made in the nitroblue tetrazolium test where the patients neutrophils fail to reduce the dye.

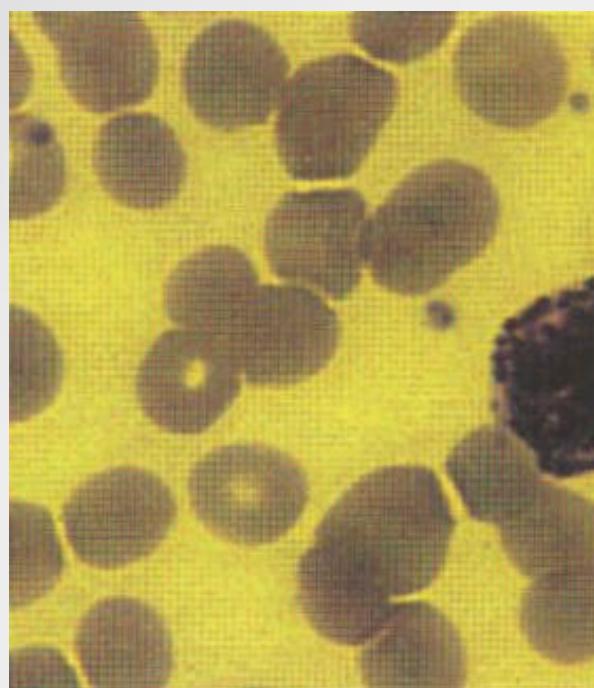


Fig. 1 a, b, c, d, e Leukocytes in the blood

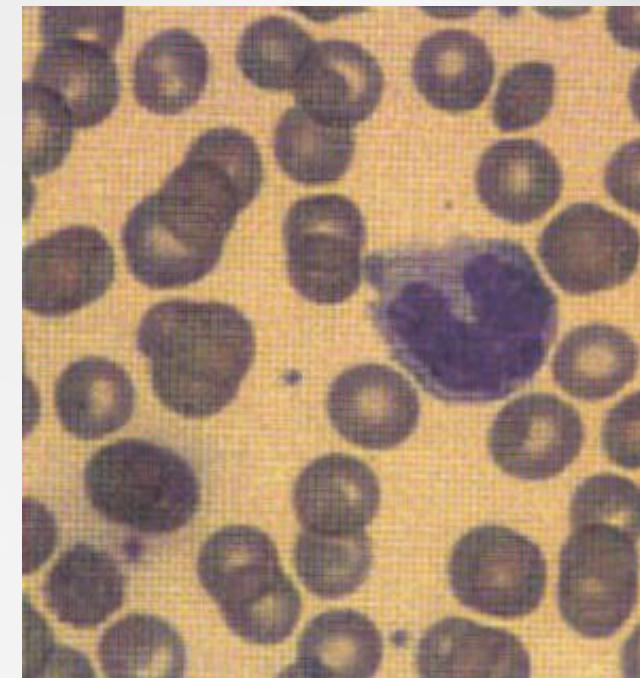


Table 1 Common causes of a neutrophil leucocytosis

Physiological (e.g. pregnancy)  
Bacterial infections  
Inflammatory diseases (e.g. vasculitis, inflammatory bowel disease)  
Trauma/surgery  
Malignancy  
Acute haemorrhage  
Severe metabolic disorders (e.g. diabetic ketoacidosis)  
Myeloproliferative diseases (e.g. chronic myeloid leukaemia)  
iatrogenic (e.g. prednisolone, growth factors)

## EOSINOPHILS

Eosinophils (Fig. 1e) are characterised by their two-lobed nucleus and red-orange staining granules. Their role is not entirely clear but like neutrophils they are attracted chemotactically and are capable of phagocytosis. They may particularly target foreign material too large for normal phagocytosis, inflicting damage by the secretion of cytotoxic enzymes.

The most common causes of eosinophilia in the Western World are allergic disorders such as asthma, eczema and hay fever. In developing countries, parasitic infections are frequently implicated. Other relatively common aetiologies are drug hypersensitivity, various skin diseases and connective tissue disorders. A marked eosinophilia is occasionally seen in association with Hodgkin's disease.

## BASOPHILS

Basophils are the least numerous of the blood leucocytes. They are easily recognised by their abundant dark purple cytoplasmic granules (Fig. 1d). The granules contain mediators of acute inflammation, including heparin and

histamine. Basophils and their tissue equivalent, mast cells, have receptors for the Fc portion of IgE. They play a central role in immediate hypersensitivity reactions. Basophilia is usually associated with myeloproliferative disorders (e.g. chronic myeloid leukaemia). However, it may be reactive to a range of systemic diseases including inflammatory bowel disease and hypothyroidism. It sometimes occurs during the recovery phase from acute infection.

## MONOCYTES

Monocytes (Fig. 1e) circulate in the blood before entering the tissues where they undergo transformation into macrophages. The 'mononuclear phagocyte' system consisting of monocytes and macrophages is a potentially confusing concept as macrophages subserve different functions and adopt discrete nomenclature in different tissues (e.g. osteoclasts in bone, Kupffer cells in liver). Macrophages are phagocytic cells but unlike neutrophils are able to survive the phagocytic event. They also act as accessory cells in the immune response by presenting antigens to T-lymphocytes (see p. 8) and secreting a wide range of cytokines involved in inflammation, immunity and haematopoiesis.

A monocytosis in the blood occurs in chronic bacterial infections such as tuberculosis and may accompany a wide range of infective, inflammatory and malignant disorders. Monocytopenia is less frequently noted but can be severe in patients receiving corticosteroid treatment.

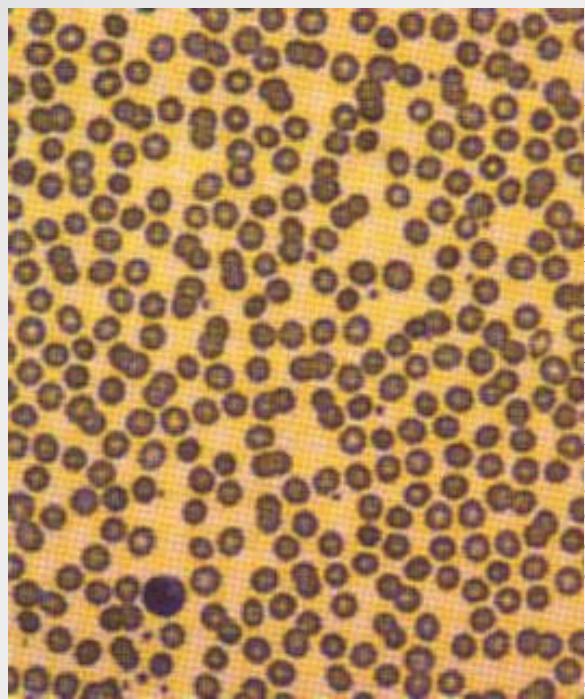
Table 2 Common causes of an isolated neutropenia

Drugs  
Idiopathic/benign/constitutional  
Autoimmune (sometimes with a connective tissue disorder)  
Infections (e.g. viral, typhoid, tuberculosis)

## Neutrophils, eosinophils, basophils and monocytes

The white cells of the blood (leucocytes) play a key role in defending the host against infection and other insults. Neutrophils, monocytes, eosinophils and basophils are phagocytes. These phagocytic cells may perform other functions; monocytes act as accessory cells presenting antigens to T-lymphocytes.

Each cell has a characteristic morphological appearance in the blood film. Changes in leucocyte numbers (e.g. neutrophil leucocytosis) are common accompaniments of various disease states.



## LYMPHOCYTES

Lymphocytes are essential for immunity. B-lymphocytes produce antibody against a specific antigen (humoral immunity) whilst T-lymphocytes are the cells of the cell-mediated response. T-lymphocytes require antigens to be presented by other cells including transformed monocytes termed macrophages. This is just one example of many interactions between leucocytes in the fight against foreign invasion.

Most mature lymphocytes appear under the light microscope as cells with round nuclei and a thin rim of agranular cytoplasm (Fig. 1). Although B- and T-cells are not distinguishable by their morphology, there are major differences in their mode of maturation and function.

**Fig. 1** Three mature lymphocytes in the blood

### T-LYMPHOCYTES

T-cells make up 75% of the lymphocytes of the blood and form the basis of cell-mediated immunity. They are less autonomous than their B-cell companions, needing the cooperation of antigen-presenting cells expressing self histocompatibility molecules (human leucocyte antigens [HLA]) for the recognition of the antigen by the T-cell receptor (TCR).

T-cells originate in the marrow but many are destroyed in subsequent processing by the thymus, the objective being to select the minority of cells which will recognise self-HLA but not react with self-tissue antigens. The maturation sequence is characterised by changing patterns of cell surface molecules. Mature T-cells are divisible into three basic types. Around two-thirds of blood T-cells are 'helper' cells expressing the surface marker CD4, whilst the remainder express CD8 and are of 'suppressor' or cytotoxic, type.

It appears that helper cells recognise the combination of antigen and self-HLA class 1 molecules on the antigen-presenting cell, and cytotoxic cells bind with antigen in conjunction with HLA class I molecules on the target cell. TCR genes, like immunoglobulin genes, are subject to rearrangement of germ-line DNA. Following triggering of T-cells by specific antigen reacting with the TCR, the clonal proliferation of activated T-cells is sustained by the secretion of cytokines. Interleukin-2 is the main T-cell growth factor.

### B-LYMPHOCYTES

B-lymphocytes are responsible for humoral immunity. Following an appropriate antigenic stimulus they transform into plasma cells and secrete antibody specific to that antigen.

B-cells are derived from the stem cells of the bone marrow. Unlike T-cells it is not clear whether they are subject to further processing at a site outside the marrow in man. Within the lymphoid tissues, such as the lymph nodes and spleen, B-cells can be stimulated by antigen to undergo a morphological transformation into immunoblasts and, ultimately, plasma cells.

Stimulation of a single B-cell by antigen combining with its cell surface immunoglobulin variable region leads to a sequence of proliferation and differentiation resulting in a clone of immunoglobulin-secreting plasma cells. Helper T-cells and cytokine-secreting macrophages facilitate this response. Memories of particular antigens are immortalised by 'memory'.

B-cells, allowing a prompt response to re-infection. The *immunoglobulins* secreted by lymphocytes and plasma cells are heterogeneous proteins, each designed to interact with a specific antigen in the defence of the body against infection (Fig. 4). There are five subclasses of immunoglobulin (Ig), dependent on the type of heavy chain (IgG, IgA, IgM, IgD and IgE) with some further division of subclasses (e.g. IgG<sub>1-4</sub>). IgM is generally produced as the initial response to infection, followed by a more prolonged production of IgG. IgA is found in secretions, whilst IgE plays a role in delayed hypersensitivity reactions.

The genes encoding the heavy and light chains of immunoglobulin are rearranged from their germ line configuration during early B-cell maturation. The variable (V), diverse (D), joining (J) and constant (C) region exons undergo a complex sequence of DNA splicing, deletions and juxtapositions. The rationale of this frenetic activity prior to transcription is to allow the totality of B-cells to produce an enormously diverse population of immunoglobulins (antibodies) targeting a vast number of potential antigens. Mistakes in gene rearrangement can lead to chromosomal translocations implicated in lymphoid malignancy.

### NATURAL KILLER (NK) CELLS

NK cells are a poorly defined subset of lymphocytes which share many of the characteristics of cytotoxic T-cells. However, NK cells are not restricted by the need for HLA identity and do not rearrange TCR genes. Killing is mediated either by direct adhesion to the target cell or by antibody dependent cell-mediated cytotoxicity (ADCC) in which the NK cell attacks the target cell via the Fc portion of antibody bound to antigen on the target cell surface. In the blood film, NK cells appear as large lymphocytes with abundant cytoplasmic granules.

### CHANGES IN DISEASE

As can be seen from Table 1 an increase in lymphocytes in the blood (lymphocytosis) is generally a reaction to infection or is part of a malignancy. A polyclonal T-cell lymphocytosis is a common response to viral infection, particularly in childhood. Lymphocytes may be morphologically abnormal with variable changes including increased size and cytoplasmic basophilia. These heterogeneous atypical lymphocytes are seen in numerous viral infections but they are a particular feature of infectious mononucleosis. Natural killer cells play a role in the response to viral and other infections, and this may manifest as an increase in large granular lymphocytes in the blood.

A number of lymphoid malignancies are associated with lymphocytosis. In acute lymphoblastic leukaemia and 'spillover' of non-Hodgkin's lymphoma cells into the blood, the malignant lymphocytes are usually morphologically distinctive and confusion with a reactive lymphocytosis rarely occurs. In chronic lymphatic leukaemia (CLL), the lymphocytes (usually B-cells) often appear unremarkable although the presence of disrupted forms, termed 'smear cells', is characteristic. CLL is the commonest form of leukaemia in many parts of the world and is frequently the cause of an otherwise unexplained lymphocytosis in an elderly person. Further tests for distinguishing between a reactive lymphocytosis and CLL are discussed on page 46.

Lymphocyte counts are often transiently low after surgery and trauma. A more chronic lymphopenia is a feature of ongoing cytotoxic drug treatment and late HIV infection when CD4 counts fall to low levels.

**Table 1** Common causes of a lymphocytosis

**Infections** Acute infections (e.g. pneumonia, infectious mononucleosis, rubella) Chronic infections (e.g. tuberculosis, toxoplasmosis)

**Malignancy** Chronic lymphatic leukaemia and variants Non-Hodgkin's lymphoma (minority)  
Acute lymphoblastic leukaemia

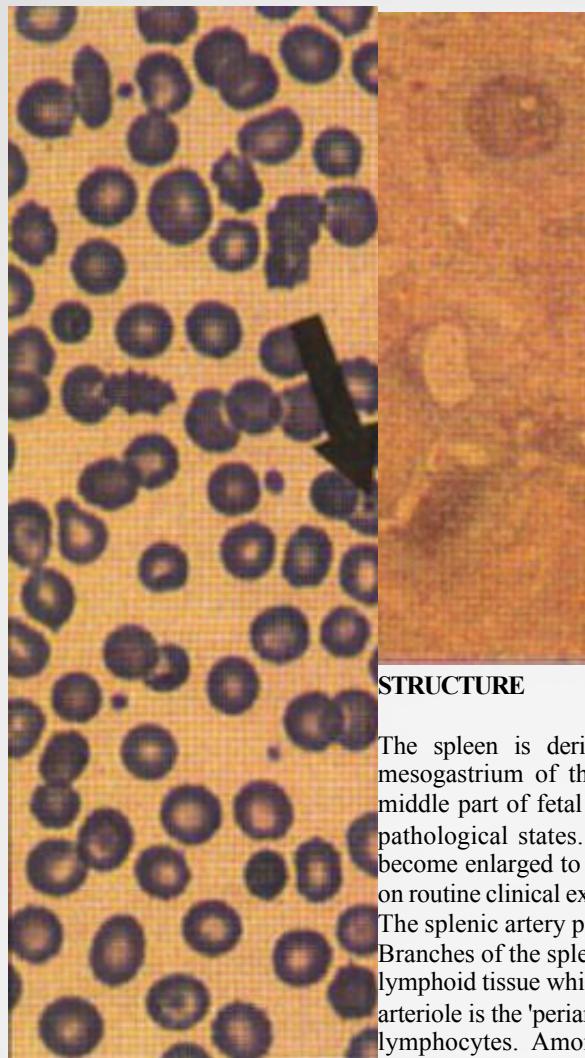
### Lymphocytes

Lymphocytes are essential for normal immunity.

B-lymphocytes respond to an appropriate antigen by transforming into plasma cells and secreting specific antibody (humoral immunity).

T-lymphocytes cooperate with antigen-presenting cells in the recognition of antigen; recognition triggers a clonal proliferation of activated T-cells (cell-mediated immunity).

The genes encoding immunoglobulin chains and the T-cell receptor are subject to rearrangement of germ-line DNA. Various disease states lead to an increase in blood lymphocyte numbers (lymphocytosis): in those over 50 years, chronic lymphatic leukaemia is the usual cause.



## THE SPLEEN

Although the spleen has been known of since ancient times its function has remained obscure until relatively recently. Hippocrates thought it was the source of 'black bile'. Galen suggested it may be a filter in view of its spongy consistency. Our current understanding of the spleen is dependent on a detailed appreciation of its vascular supply and the organisation of its main component parts: the white pulp, the red pulp and the intervening marginal zone.

**Fig. 1** Light microscopy of the spleen clearly showing the distribution of red and white pulp.

### STRUCTURE

The spleen is derived from condensation of the mesoderm in the dorsal mesogastrium of the embryo. It plays a modest haematopoietic role in the middle part of fetal life, but in the adult haematopoiesis is usually only seen in pathological states. An average adult spleen weighs about 150g and it has to become enlarged to at least three times its normal size before becoming palpable on routine clinical examination.

The splenic artery penetrates the thick capsule which invests the organ. Branches of the splenic artery are surrounded by a highly organised aggregate of lymphoid tissue which is termed the 'white pulp'. Intimate to the central arteriole is the 'periarteriolar lymphatic sheath' - an area mainly populated by T-lymphocytes. Amongst these T-lymphocytes are nonphagocytic, antigen-presenting cells known as 'interdigitating cells'. Spaced at intervals in the

periarteriolar lymphatic sheath are lymphoid follicles ('Malpighian bodies'). In an inactive state these follicles are composed of recirculating B-lymphocytes intertwined with cytoplasmic processes of follicular dendritic cells. The latter cells may play a role in long-term antibody production. When contact with antigen stimulates B-cell activation a germinal centre of rapidly dividing cells forms in the follicle. This is a key area in the normal B-lymphocyte proliferative response and development of B-cell memory.

The periarteriolar lymphatic sheath and B-lymphocyte follicles are separated from the red pulp by a 'marginal zone' constituted mainly of non-circulating B-cells. The marginal zone also contains specialised macrophages able to take up carbohydrate antigens. The red pulp is composed of two alternating structures: the splenic sinuses and the splenic cords (the 'cords of Billroth'). The cords are a reticular meshwork packed with macrophages and antibody secreting plasma cells. The sinuses are broad channels lined with fusiform endothelial cells.

Most of the central arterioles open into the marginal zone. As alluded to already, circulating T-lymphocytes move into the periarteriolar lymphatic sheath and B-lymphocytes migrate to the follicles. Other blood cells move slowly through the complex meshwork of the red pulp and cells which are sufficiently deformable and compliant squeeze between the endothelial cells in the sinus wall into the lumen of the sinus and back into the circulation. A small component of the splenic blood flow (the 'fast component') bypasses this slow filtration through the red pulp and passes directly into the splenic sinuses.

### FUNCTION

The spleen has two major general functions: it removes unwanted material from the blood as well as from within red cells it has an important role in the immune system.

**Fig. 1** The blood film in hyposplenism. There are target cells and acanthocytes

The spleen removes unwanted red cells and particles from the blood in three ways. Firstly, they can be removed by phagocytes. Bacteria, particularly encapsulated organisms that are not opsonised by antibodies and complement, are cleared from the circulation. The spleen is probably the site of the initial immune response to these organisms. Phagocytic cells in the spleen also remove red cells coated with IgG antibody.

The second mechanism at work is the removal of red cells which are not sufficiently deformable to pass through the sinus wall. Pathological states where red cells lose deformability and are destroyed prematurely in the spleen include sickle cell anaemia, hereditary spherocytosis and malaria.

Finally, the spleen can remove debris or organisms from within cells. Howell-Jolly bodies (fragments of nucleus) and malarial parasites are removed when most of the cell passes

through the inter-endothelial slit with the intracellular particle abandoned on the cord side.

In addition to its filtration function the spleen has the capacity to produce antibodies. The splenic marginal zone B-lymphocytes may be a source of antibodies to polysaccharide antigens.

### ABNORMAL SPLENIC STATES

The syndromes arising out of splenic hypofunction and enlargement give additional insights into the normal role of the spleen.

#### Asplenism and Hyposplenism

Surgical removal of the spleen (splenectomy) may be indicated in a variety of haematological disorders and following trauma. The spleen may also be absent as a congenital anomaly, often associated with transpositions or malformations of the great vessels and viscera ('asplenia syndrome'). Reduced splenic function can result from splenic atrophy in disorders such as sickle cell anaemia, adult coeliac disease and essential thrombocythaemia (Table 1).

**Table 1 Causes of hyposplenism**

Congenital absence of spleen
Splenectomy
Sickle cell anaemia
Coeliac disease
Essential thrombocythaemia
Dermatitis herpetiformis
Inflammatory bowel disease

Hyposplenism leads to characteristic changes in the blood film. Changes in red cell appearance include the presence of Howell-Jolly bodies, Pappenheimer (siderotic) granules and target cells. Other less regular red cell features are lipid-rich acanthocytes and circulating nucleated cells. There is often a moderate rise in the lymphocyte, monocyte and platelet count. Approximately one-third of circulating platelets are pooled in the normal spleen. The increase in platelets post-splenectomy is frequently impressive (greater than  $1000 \times 10^9/l$ ) but the count usually falls to a lower level in the longer term.

The haematological changes are a useful guide to the presence of hyposplenism but the clinical significance of an absent spleen is the associated increased risk of life-threatening infection. The risk is greatest in children under five years of age and where there is a serious underlying medical disorder such as Hodgkin's disease or thalassaemia.

Most infections occur within 2 years of splenectomy but fulminating infection can strike at any stage. In most cases infection is with encapsulated bacteria, notably *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. In temperate regions more than half of serious infections are caused by the pneumococcus, with high mortality. Splenectomised patients have an increased susceptibility to severe malaria. Prophylaxis against such infections is evidently the best approach and recommendations for the management of asplenic patients are shown in Table 2.

## Hypersplenism

Hypersplenism is usually defined as a depression of one or more of the cell counts in the blood which can be wholly attributed to splenic enlargement. Other criteria such as the presence of a normal bone marrow, or correction of cytopenia by splenectomy may be appended. Although the definition only requires an isolated anaemia, leucopenia or thrombocytopenia, there is frequently a moderate pancytopenia.

Splenomegaly is not always associated with hypersplenism, and hypersplenism can occur irrespective of the degree of splenic enlargement. Thus, it may be seen in the modest splenomegaly of liver cirrhosis.

The pancytopenia of hypersplenism is probably induced by three contributory mechanisms:

Hypervolaemia consequent upon a disproportionately expanded plasma volume filling the vascular space of the enlarged spleen and the splanchnic bed.

Intraspionic pooling of red cells which is increased from the normal 5-15% to 40% in moderate splenomegaly. This is accompanied by pooling of neutrophils and platelets.

Premature destruction of circulating blood cells.

Table 2 Management recommendations in the asplenic patient

<b>Immunisation</b>	Against <i>Pneumococcus, Haemophilus and Meningococcus</i>
<b>Antibiotic prophylaxis</b>	Oral penicillin V 250 mg bd
<b>Prompt treatment of infection</b>	Patient keeps course of antibiotics to avoid possible delay in treatment
<b>Medicalert disc or card</b>	Detailing asplenic state and medical contacts
<b>Avoid travel to high risk malarial areas</b>	

Where possible at least two weeks prior to splenectomy. Reimmunisation is usually required, the timing determined by measurement of specific antibody levels.

The duration of antibiotic prophylaxis is controversial: probably at least up to 18 years in children and at least 5 years in adults.

Amoxycillin is first choice in children less than 5 years old and erythromycin at any age where there is penicillin allergy.

## The spleen

The spleen is organised into three main components: the white pulp, the red pulp and the intervening marginal zone. The spleen acts as a filter, removing unwanted red cells and particles from the blood. The spleen plays a role in the immune response producing antibodies.

An absent or poorly functioning spleen leads to characteristic blood changes and an increased risk of overwhelming infection, including fulminating malaria.

An enlarged spleen (splenomegaly) may cause 'hypersplenism' with reduced cell counts in the blood.

## HAEMOSTASIS

The clotting of blood is a critical defence mechanism which, in conjunction with inflammatory and general repair responses, helps protect the integrity of the vascular system after injury. The complex sequence of events described in detail below is activated within seconds of tissue damage. Both cells (particularly platelets) and plasma proteins play essential roles in the haemostatic mechanism. It is easiest to divide the description of normal haemostasis into a platelet component, with formation of a loose platelet plug at the site of injury, and a coagulation component where there is generation of a more robust fibrin scaffold (thrombus) around the platelets. This approach facilitates understanding but in practice the two are inextricably linked.

### THE ROLE OF PLATELETS

Following damage to a blood vessel there is immediate vasoconstriction to slow blood flow and reduce the risk of exsanguination. The break in the endothelial cell barrier leads to the recruitment of platelets from the circulation to form an occlusive plug. Platelets interact both with the vessel subendothelial matrix (platelet 'adhesion') and with each other (platelet aggregation'). The first step in this process, adhesion, does not require platelet metabolic activity. It does, however, lead to the activation' of platelets.

Platelets are small disc-shaped particles produced in megakaryocyte cytoplasm. They have no nucleus and no capacity for DNA biosynthesis but do have a complex infrastructure. Pores in the trilaminar platelet membrane connect with an open canalicular system allowing transport of agonists in and discharge of secretions out. The membrane receptors for agonists include:

the glycoprotein (gp) Ia/IIa complex which is a receptor for collagen  
the gpIb/IX complex, a receptor for vessel wall von Willebrand's factor (vWF) and thrombin

the gpIIb/IIIa complex which is an agonist-induced receptor for fibrinogen and vWF.

In the platelet cytoplasm are organelles including alpha granules (containing fibrinogen, vWF, thrombospondin and other proteins) and dense granules (containing small molecules such as ADP and calcium).

Platelet activation follows stimulation by agonists such as ADP and thrombin interacting with surface receptors, or by direct contact with the vessel wall

subendothelial matrix. The changes occurring during platelet activation are shown schematically in Figure 1. Platelets convert from a compact disc to a sphere, surface receptors become activated, and cytoplasmic granules secrete their contents. The net effect is the mediation and reinforcement of aggregation and adhesion, and the promotion of further activation. Other circulating platelets adhere to the initial layer and a loose platelet plug is formed.

In addition to the formation of a physical barrier at the site of injury platelets have a *procoagulant action*. The coagulation sequence described below completes much more rapidly in the presence of platelets. Following activation, platelets rearrange their membrane phospholipids and shed vesicles from their surface. The platelet surface and vesicles reveal binding sites for coagulation proteins leading to the creation of coagulation complexes (e.g. the 'prothrombinase complex') which accelerate formation of Factor  $X_a$  and thrombin.

## COAGULATION

Although often loosely used to encompass all aspects of clot formation the term 'coagulation' more specifically refers to the mechanism directly leading to the conversion of the soluble plasma protein fibrinogen to the insoluble rigid polymer fibrin. The formation of the stable haemostatic plug composed of enmeshed fibrin and platelets is the culmination of a complex biochemical cascade involving circulating *coagulation factors*. This system allows extreme amplification with a robust thrombus arising from the initial stimulus of tissue injury. Most activated coagulation factors are proteolytic enzymes (serine proteases) which in the presence of cofactors cleave other factors in an ordered sequence. Thus, prothrombin (Factor 11), Factor VII, Factor IX and Factor X are proenzymes which are converted to their active enzyme form (denoted by the subscript 'a') by cleavage of one or two peptide bonds. Factors V and VIII are procofactors which are converted to the active cofactors (V. and VIII.) also by cleavage of peptide bonds. The blood clotting proenzymes prothrombin and Factors VII, IX and X require vitamin K for their activation.

The coagulation cascade, leading to the generation of thrombin and the formation of a fibrin thrombus, is classically divided into two parts: the intrinsic and extrinsic pathways (Table 1).

In the intrinsic pathway Factor XII is activated by exposed collagen and other negatively charged components of the subendothelium. Activation of Factor XII leads to the sequential activation of Factors XI, IX, VIII (as cofactor), X and prothrombin. In the extrinsic pathway tissue factor complexes with Factor VII with sequential activation of Factors VII, X and prothrombin. Both intrinsic and extrinsic pathways terminate in the final common pathway where activated Factor

X, in association with the cofactor Factor V, in the presence of phospholipid and calcium, converts prothrombin into thrombin. Thrombin in turn converts fibrinogen to fibrin by splitting the fibrinopeptides A and B from the centre domain to form fibrin monomers. These monomers combine spontaneously into dimers which assemble to form the fibrin polymer. Factor XIII crosslinks the fibrin polymer to consolidate the thrombus. The final fibrin thrombus forms a meshwork which reinforces the platelet plug. It is fully strengthened by other adhesive proteins including thrombospondin, fibrinonectin and platelet fibrinogen. The conventional division into two pathways is useful in the interpretation of *in vitro* laboratory tests of haemostasis.

The prothrombin time (PT) is a simple measure of the function of the extrinsic pathway and the activated partial thromboplastin time (APTT) monitors the intrinsic pathway. However, the physiological pathways at work *in vivo* are not so simply defined. It seems that the intrinsic pathway is rarely relevant to coagulation *in vivo* - patients with a hereditary deficiency of Factor XII have a prolonged APTT but no bleeding disorder. The crucial protein in the initiation of blood coagulation is tissue factor. Tissue factor is an integral membrane protein expressed on non-vascular cells. The tissue factor-Factor VII complex activates not only Factor X (the extrinsic pathway) but also Factor IX (the alternative pathway).

## Regulation of coagulation

Blood clotting is a vital defence mechanism. However, it is important that coagulation is not allowed to become generalised with occlusion of vessels. Several regulatory mechanisms are in place. There are inhibitors of coagulation circulating in the plasma:

**Anti-thrombin III.** This is the most important inhibitor of the terminal proteins of the cascade, particularly Factor  $X_a$  and thrombin. Its activity is greatly increased by interaction with heparin in the microvasculature and on the surface of endothelial cells.

**Proteins C and S.** Protein C is a vitamin K dependent plasma protein which inactivates the cofactors V and VIII and stimulates fibrinolysis. Protein C is converted to its active enzymic form by interaction with thrombin. Protein S acts as a cofactor for Protein C

In addition to these naturally occurring anticoagulants there is routine system for thrombus digestion - the fibrinolytic system.

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Haemostasis

Once damaged endothelium is repaired the fibrin thrombus must be removed to restore normal blood flow. Thrombus removal is facilitated by a fibrin-splitting serine protease, plasmin. The fibrinolytic system is shown schematically in Figure 3. Release of tissue plasminogen activator (t-PA) from endothelial cells leads to conversion of the proenzyme plasminogen into plasmin. t-PA is most active when bound to fibrin thus maximising its action at the site of the thrombus. Plasmin has the capacity to digest fibrin in addition to fibrinogen and a number of other proteins. Digestion of a cross-linked thrombus by plasmin leads to the formation of 'degradation products' which themselves act as anticoagulants. Fibrinolysis is under strict control; circulating plasmin is inactivated by the protease inhibitor  $\alpha_2$ -antiplasmin.

The clotting of blood is a critical defence mechanism p integrity of the vascular system after injury.

Platelets form an occlusive plug at the site of tissue injury. They also have procoagulant action.

The term 'coagulation' describes the process by which fibrinogen is converted to the insoluble rigid polymer fibrin; the final thrombus is formed of enmeshed fibrin and platelets.

The term 'coagulation cascade' describes the sequential activation of coagulation factors; in vivo the major initiator of coagulation is tissue factor.

Fibrin generation is regulated by naturally occurring anticoagulants and fibrin is ultimately removed by the 'fibrinolytic system'.

## **ANAEMIA**

### **INTRODUCTION AND CLASSIFICATION**

#### **DEFINITION**

The term 'anaemia' refers to a reduction of haemoglobin or red cell concentration in the blood. With the widespread introduction of automated equipment into haematology laboratories the haemoglobin concentration has replaced the haematocrit (or 'packed cell volume') as the key measurement. Haemoglobin concentration can be determined accurately and reproducibly and is probably the laboratory value most closely correlated with the pathophysiological consequences of anaemia. Thus, anaemia is simply defined as a haemoglobin concentration below the accepted normal range.

The normal range for haemoglobin concentration varies in men and women and in different age groups (Table 1). The definition of normality requires accurate haemoglobin estimation in a carefully selected reference population. Subjects with iron deficiency (up to 30% in some unselected populations) and pregnant women must be excluded or the lower level of normality will be misleadingly low. Normal haemoglobin ranges may vary between ethnic groups and between populations living at different altitudes.

#### **PREVALENCE**

The prevalence of anaemia and the aetiologies vary in different populations. In developed countries where most studies have been performed, anaemia is more common in women than in men. Particularly susceptible groups include pregnant women, children under 5 years and those on low income. The majority of cases are caused by iron deficiency. In developing countries, factors influencing the prevalence of anaemia include climate, socio-economic conditions and, most importantly, the incidence of co-existent diseases.

#### **GENERAL FEATURES**

In anaemia the blood's reduced oxygen carrying capacity can lead to tissue hypoxia. The clinical manifestations of significant anaemia are to a large extent due to the compensatory mechanisms mobilised to counteract this hypoxia. Cardiac overactivity causes palpitations, tachycardia and heart murmurs. The dyspnoea of severe anaemia may be a sign of incipient cardiorespiratory failure. Pallor is due primarily to skin vasoconstriction with redistribution of blood flow to tissues with higher oxygen dependency such as the brain and myocardium.

Anaemia is one of the most common clinical problems presenting in general practice, hospitals and in medical examinations. Usually characteristic symptoms and signs prompt a blood count to confirm the diagnosis but on occasion an unexpectedly low haemoglobin estimation in a 'routine' blood count precedes the clinical consultation. Whatever the sequence of events, anaemia is not in itself an adequate diagnosis; further enquiry to establish the underlying cause is essential.

A logical approach to anaemia demands a clear understanding of both its possible causes and its clinical and laboratory features. There are two major classifications- both have advantages and they are best used together.

Table 1 Normal haemoglobin concentrations at different ages

Age	Mean haemoglobin (g/l)	Lower limit of normal (g/l)
Birth (cord blood)	165	135
1-3 days (capillary)	185	145
1 month	140	100
2-6 months	115	95
6 months-2 years	120	105
2-6 years	125	115
-6-12 years	135	115

12-18 years		
Female	140	120
Male	145	130
Adult		
Female	140	115
Male*	155	135

### **CLASSIFICATION**

#### **Morphological classification**

As already discussed, modern electronic laboratory equipment can provide estimations of red cell indices in addition to haemoglobin concentration. Abnormal red cell indices should be confirmed by microscopic examination of blood films. The 'morphological' classification is based on a correlation between red cell indices and the underlying cause of anaemia. The most important measurements are of red cell size (mean cell volume or MCV) and red cell haemoglobin concentration (mean cell haemoglobin [MCH] or mean cell haemoglobin concentration [MCHC]). Anaemias with raised, normal and reduced red cell size (MCV) are termed macrocytic, normocytic and microcytic respectively. Anaemias associated with a reduced haemoglobin concentration within red cells are termed hypochromic and those with a normal MCH are termed normochromic. Characteristic combinations are of microcytosis and hypochromia, and normocytosis and normochromia. As can be seen in Figure 1 this terminology is helpful in narrowing the differential diagnosis of anaemia. It is perhaps least helpful in normocytic anaemia as the possible causes are numerous and diverse.

The value of the blood film in diagnosis should not be underestimated. For instance, combined iron deficiency (a cause of microcytosis) and folate deficiency (a cause of macrocytosis) may cause an anaemia with a normal MCV. However, inspection of the film will reveal a dual population of microcytic hypochromic red cells and macrocytic red cells.

#### **Aetiological classification**

Figure 2 illustrates a classification of anaemia based on cause. It is less immediately helpful than the morphological classification in forming a differential diagnosis but it does illuminate the pathogenesis of anaemia. The fundamental division is between excessive loss or destruction of mature red cells, and inadequate production of red cells by the marrow.

Loss of red cells occurs in haemorrhage and excessive destruction in haemolysis. A normal bone marrow will respond by increasing red cell production with accelerated discharge of young red cells (reticulocytes) into the blood. Inadequate red cell production may result from insufficient erythropoiesis (i.e. a quantitative lack of red cell precursors) or ineffective erythropoiesis (i.e. defective erythrocytes destroyed in the marrow). Examples of insufficient erythropoiesis include bone marrow hypoplasia as in aplastic anaemia, and infiltration of the marrow by a leukaemia or other malignancy. Inefficient erythropoiesis is seen in disorders such as megaloblastic anaemia, thalassaemia and myelodysplastic syndromes.

The above provides a useful framework for thinking about anaemia. In reality different mechanisms can operate simultaneously, e.g. the anaemia of thalassaemia is caused by both ineffective erythropoiesis and haemolysis.

### **MANAGEMENT**

The treatment of specific types of anaemia is discussed in subsequent sections. However, some general statements can be made. Whenever possible, the cause of anaemia should be determined before treatment is instituted. Blood transfusion should only be used where the haemoglobin is dangerously low, where there is risk of a further dangerous fall in haemoglobin (e.g. rapid bleeding), or where no other effective treatment of anaemia is available. Prompt blood transfusion can be life-saving in a profoundly anaemic patient but it should be undertaken with great caution as heart failure can be exacerbated.

### **Introduction and classification**

Anaemia is defined as a haemoglobin concentration below the accepted normal range.

The normal range for haemoglobin is affected by sex, age, ethnic group and altitude.

The clinical features of anaemia are largely caused by compensatory measures mobilised to counteract hypoxia.

Anaemia can be classified according to red cell morphology or aetiology.

Red cell indices and morphology correlate with the underlying cause of anaemia.

Wherever possible the cause of anaemia should be determined before treatment is started. Blood transfusion is only required in a minority of cases.

## IRON DEFICIENCY ANAEMIA

### IRON

Iron is a constituent of haemoglobin and rate limiting for erythropoiesis. The metabolism of iron in the body is dominated by its role in haemoglobin synthesis (Fig. 1). Normally, the total iron content of the body remains within narrow limits: absorption of iron from food must replace any iron losses. Iron is not excreted as such but is lost in desquamated cells, particularly epithelial cells from the gastrointestinal tract. Menstruating women will lose an additional highly variable amount of iron, and in pregnancy the rate of iron loss is about 3.5 times greater than in normal men. The storage forms of iron, ferritin and haemosiderin, constitute about 30% of body iron stores.

### IRON DEFICIENCY

Clinically significant iron deficiency is characterised by an anaemia which can usually be confidently diagnosed on the basis of the clinical history and blood count. It cannot be overstressed that the diagnosis of iron deficiency is not adequate in itself - a cause for the deficiency must always be sought.

### CAUSES

The likely cause will vary with the age, sex and geographic location of the patient (Table 1). Iron deficiency is usually caused by long-term blood loss, generally due to gastrointestinal or uterine bleeding and less commonly to bleeding in the urinary tract or elsewhere. Particularly in elderly patients, deficiency may be the presenting feature of gastrointestinal malignancy. Hookworm infection is the commonest cause of iron deficiency worldwide. Malabsorption and increased demand for iron as in pregnancy are other possible causes. Poor diet may exacerbate iron deficiency but is rarely the sole cause outside the growth spurts of infancy and teenage years.

### CLINICAL FEATURES

These can be conveniently grouped into three categories:

#### General symptoms and signs of anaemia

**Symptoms and signs specific to iron deficiency.** Iron is required by many tissues in the body, shortage particularly affecting endothelial cells. Patients with long-standing deficiency *may develop* nail flattening and koilonychia (concave nails), sore tongues and papillary atrophy, angular stomatitis, dysphagia due to an oesophageal web (Plummer-Vinson syndrome) and a gastritis which is usually symptomless. Many patients show none of these features and their absence is thus of little significance. Iron deficiency in young children can contribute to psychomotor delay and behavioural problems.

**Symptoms and signs due to the underlying cause of iron deficiency.** Patients may spontaneously complain of heavy periods, indigestion or a change in bowel habit. Once the diagnosis of iron deficiency is known, it is often useful to retake the history and re-examine the patient with a view to detecting any clue of an underlying disorder. Rectal examination should be routine.

Table 1 Causes of iron deficiency

#### Very Common

Bleeding from the gastrointestinal tract  
(e.g. benign ulcer, malignancy)

Menorrhagia

#### Other

Pregnancy  
Malabsorption (e.g. coeliac disease)  
Malnutrition  
Bleeding from urinary tract  
Pulmonary haemosiderosis

## DIAGNOSIS

The diagnosis may be suspected on the basis of the history and examination but laboratory investigations are required for confirmation.

### The blood count

Iron deficiency causes a hypochromic microcytic anaemia. The automated red cell analyser generates a report with haemoglobin, MCV and MCH values below the normal range. There is a variation in red cell size (anisocytosis) reflected by a high red cell distribution width (RDW). A blood film will show characteristic features.

### Confirmatory tests

Further tests are helpful in confirming the diagnosis (Table 2) and excluding other causes of a hypochromic microcytic anaemia. Measurement of serum ferritin is probably the most useful of these tests: a low level always indicates iron deficiency but a normal level does not guarantee normal stores as ferritin is increased in chronic inflammation and liver disease. In occasional difficult cases (e.g. where the patient has recently been transfused) a bone marrow aspirate is helpful in showing absence of iron stores. In practice the most likely confusion is with the anaemia of chronic disorders.

## MANAGEMENT

This is divisible into investigations of the underlying cause and the correction of iron deficiency.

### Investigation of underlying cause

Where the likely cause is apparent, further investigations can be highly selective. Thus in a young woman with severe menorrhagia and no other symptoms it can be assumed that uterine bleeding is the cause of iron deficiency, and investigation of the gastrointestinal tract is not necessary. A gynaecological referral would be adequate. Complaints of indigestion or a change in bowel habit should prompt an endoscopy or a colonoscopy or barium enema as first investigations. However, often there are no symptoms suggesting a site of blood loss. As the gastrointestinal tract is the most common site in men and postmenopausal women, stool samples can be taken to check for occult blood (faecal occult bloods or FOBs). Persistent positivity is a good indicator of bleeding but negative results do not entirely exclude it.

A reasonable approach to this common problem is to commence with colonoscopy and, if normal, to proceed to upper GI endoscopy. If upper GI endoscopy is performed first in an elderly patient and shows a benign ulcerative lesion then assessment of the lower GI tract should probably still be performed as coexistent colonic neoplasms are found in a significant minority of cases. If the GI tract is normal, the urine can be screened for haematuria and a chest X-ray checked to exclude the rare diagnosis, pulmonary haemosiderosis. In 20% of cases of iron deficiency no cause is found.

Table 2 Tests to confirm iron deficiency

Test	Result in iron deficiency	Comment
Ferritin	Low	Level increased in chronic inflammation/liver disease
Transferrin saturation	Low	Low levels also in elderly and chronic disease
Serum iron	Low	Levels fluctuate significantly and low in chronic disease
TIBC	High	Useful test as low in anaemia of chronic

Zinc protoporphyrin	High	disease
BM iron	Low	Late finding only
Serum transferrin receptor level	High	Informative but invasive investigation
TIBC, total iron binding capacity; BM, bone marrow		Also high in haemolysis
<b>Correction</b>		
Oral iron is given to correct the anaemia. The normal regimen is ferrous sulphate 200 mg three times a day (providing 180 mg elemental iron daily). Side-effects, including nausea, epigastric pain, diarrhoea and constipation, are best managed by reducing the dosage rather than changing the preparation. An adequate response to oral iron is an increase in haemoglobin of 20 g/l every 3 weeks. Iron is given for at least 6 months to replete body stores. There are several possible causes of a failure to respond to oral iron (Table 3). Intramuscular iron may occasionally be used in patients who are intolerant of oral iron or malabsorb it, or where it is necessary to rapidly replenish body stores (e.g. in late pregnancy). Intravenous infusion of iron is rarely indicated. It must be given under close supervision as anaphylaxis can occur.		

Table 3 Failure to respond to oral iron possible causes

Wrong diagnosis (i.e. other cause of anaemia)  
Non-compliance  
Malabsorption  
Continued bleeding

### Iron deficiency anaemia

Iron is a constituent of haemoglobin and is essential for erythropoiesis.

Iron deficiency is most often caused by long-term blood loss.

Iron deficiency causes a hypochromic microcytic anaemia.

The anaemia is usually easily corrected with oral iron supplements.

It is important to establish the cause of iron deficiency - it may be the presenting feature of gastrointestinal malignancy.

## MEGALOBLASTIC ANAEMIA

The megaloblastic anaemias are characterised by delayed maturation of the nucleus of red cells in the bone marrow due to defective synthesis of DNA. Red cells either die in the marrow ('ineffective haematopoiesis') or enter the bloodstream as enlarged, misshapen cells with a reduced survival time. In clinical practice megaloblastic anaemia is almost always caused by deficiency of vitamin B<sub>12</sub> (cobalamin) or folate (pteroylmono-glutamate). It is one of the most common causes of a macrocytic anaemia.

### VITAMIN B<sub>12</sub> AND FOLATE

Key characteristics of these essential vitamins are summarised in Table 1. Vitamin B<sub>12</sub>, deficiency most commonly arises from malabsorption whilst folate deficiency is more often due to frank dietary deficiency or increased dietary requirements, as in pregnancy.

### WHY DOES DEFICIENCY OF VITAMIN B<sub>12</sub>, OR FOLATE LEAD TO MEGALOBLASTIC ANAEMIA?

Both folate and vitamin B<sub>12</sub> are necessary for the synthesis of DNA. Folate is needed in its tetrahydrofolate form (FH<sub>4</sub>) as a cofactor in DNA synthesis. Deficiency of B<sub>12</sub> leads to impaired conversion of homocysteine to methionine causing folate to be 'trapped' in the methyl form. The resultant deficiency in methylene FH<sub>4</sub> deprives the cell of the coenzyme necessary for DNA formation.

All dividing cells in the body suffer from the impaired DNA synthesis of B<sub>12</sub> and folate deficiency. However, the actively proliferating cells of the bone marrow are particularly affected. As RNA synthesis progresses unhindered in the cytoplasm the erythroid cells develop nuclear-cytoplasmic imbalance with abundant basophilic cytoplasm and enlarged nuclei. The chromatin pattern in the nucleus is characteristically abnormal; one author has described it as resembling 'fine scroll work', another as 'sliced salami'. The slow-down in synthesis of DNA leads to prolonged cell cycling and the cells being discharged into the blood without the normal quota of divisions. Thus the red cells are enlarged and egg shaped and the neutrophils hypersegmented due to retention of surplus nuclear material.

Table 1 Vitamin B<sub>12</sub> and folate

Characteristic	Vitamin B <sub>12</sub>
Average dietary intake/day (mcg)	20
Minimum adequate intake/day (mcg)	1-2
Major food sources	Animal produce
Normal body stores	Sufficient for 2 years
Mode of absorption	Combined with intrinsic factor secreted by gut absorbed through ileum via special receptors

500mcg daily required in pregnancy THF: Tetrahydrofolate

### CLINICAL SYNDROMES

#### VITAMIN B<sub>12</sub> DEFICIENCY

##### Pernicious anaemia

This classical cause of vitamin B<sub>12</sub> deficiency is an autoimmune disorder. The majority of patients have IgG autoantibodies targeted against gastric parietal cells and the B<sub>12</sub> transport protein intrinsic factor. The precise pathogenesis, and particularly the role of the autoantibodies, is incompletely understood but B<sub>12</sub> deficiency ultimately arises from reduced secretion of intrinsic factor (IF) by parietal cells and, hence, reduced availability of the B<sub>12</sub>-IF complex which is absorbed in the terminal ileum.

The clinical hallmarks of pernicious anaemia are gastric parietal cell atrophy and achlorhydria, a more generalised epithelial cell atrophy and megaloblastic anaemia. The disease is most common in Northern Europe in women greater than 50 years of age and is familial. Affected patients classically have premature greying of the hair and blue eyes and may develop other autoimmune disorders including vitiligo, thyroid disease and Addison's disease. Slight jaundice is caused by the haemolysis of ineffective erythropoiesis.

Patients usually have symptoms of anaemia and the generalised epithelial abnormality can manifest as glossitis and angular stomatitis. The archetypal neurological syndrome of pernicious anaemia - 'subacute combined degeneration' - arises from demyelination of the dorsal and lateral columns of the spinal cord. Patients most commonly complain of an unsteady gait, and if B<sub>12</sub> deficiency is not corrected there can be progression to irreversible damage of the central nervous system and bladder disturbance. There is an increased incidence of carcinoma of the stomach in patients with pernicious anaemia.

##### Diagnosis.

The normal sequence of investigations is as follows:

1. *Blood count and film.* There is a macrocytic anaemia with the typical film appearance of megaloblastic anaemia. There may be leucopenia and thrombocytopenia.

2. *Bone marrow aspirate.* This is not always necessary. It will confirm megaloblastic anaemia but will not illuminate the underlying cause.

3. *Estimation of vitamin B<sub>12</sub> and folate, levels.* Normal methodologies include immunoassay techniques. In pernicious anaemia the serum vitamin B<sub>12</sub> level is normally very low. The serum folate may be elevated and the red cell folate reduced (folate is trapped in its extracellular methyl FH<sub>4</sub> form).

4. *Autoantibodies.* Parietal cell antibodies are found more commonly in the serum than IF antibodies (90% vs 50%) but whereas IF antibodies are almost diagnostic of pernicious anaemia, parietal cell antibodies occur in about 15% of healthy elderly people. The antibodies may also be detected in gastric juice.

5. *Tests for vitamin B<sub>12</sub> absorption.* Patients swallow B<sub>12</sub> labeled with radioactive cobalt and absorption is usually measured indirectly by quantifying urinary excretion (Schilling test). If malabsorption is corrected by adding IF to the oral dose, pernicious anaemia is the likely cause.

**Treatment.** Vitamin B<sub>12</sub> levels are replenished by intramuscular injection of the vitamin. Several injections of 1 mg hydroxycobalamin are given over the first few weeks and then one injection every 3 months for life. The increase in reticulocytes in the blood peaks 6 to 7 days after the start of treatment.

In practice patients with megaloblastic anaemia are often started on both B<sub>12</sub> and folate supplements after a blood sample has been taken for assay of the vitamins.

When the results are known the unnecessary vitamin can be stopped. Blood transfusion is best avoided as it may lead to circulatory overload where judged necessary to correct hypoxia it is undertaken with extreme caution. Hypokalaemia occasionally requires correction.

**Other causes of Vitamin B<sub>12</sub> deficiency** As B<sub>12</sub> absorption depends on IF secretion by gastric parietal cells and a normal ileum it follows that abnormalities of the stomach or ileum may cause deficiency. Dietary deficiency is rare and usually restricted to vegans. As normal body stores are sufficient for 2 years, clinically apparent deficiency from any cause will develop slowly.

### FOLATE DEFICIENCY

Folate deficiency is caused by dietary insufficiency, malabsorption, excessive utilisation or a combination of these. Patients may complain of symptoms of anaemia or of an underlying disease. Initial investigations are as for pernicious anaemia with a macrocytic anaemia and a megaloblastic bone marrow. Detection of folate deficiency is slightly complicated by the availability of assays for both serum and red cell levels. In significant deficiency both are usually low but the red cell folate is the better measure of tissue folate stores. In addition to a thorough dietary history patients may need investigations for malabsorption (e.g. jejunum biopsy).

Folate deficiency is treated with oral folic acid 5mg once daily. This is given for several months at least, the precise duration of therapy depending on the underlying cause. Folate is prescribed prophylactically in pregnancy (400 mcg daily) and in groups of patients at high risk of deficiency (Table 2). Before folate is prescribed, vitamin B<sub>12</sub> deficiency must be excluded (or corrected) as subacute combined degeneration of the cord can be precipitated.

### Megaloblastic anaemia

Megaloblastic anaemia is a common cause of a macrocytic anaemia.

In clinical practice it is almost always caused by deficiency of vitamin B<sub>12</sub> or folate.

Vitamin B<sub>12</sub> deficiency normally arises from malabsorption – the classical clinical syndrome is the autoimmune disorder pernicious anaemia.

Folate deficiency is more often due to frank dietary deficiency or increased dietary requirements as in pregnancy.

Vitamin B<sub>12</sub> deficiency should be excluded or corrected before folate is administered as subacute combined degeneration of the cord can be precipitated.

Table 2 The megaloblastic anaemias

#### Vitamin B<sub>12</sub> deficiency

Deficiency of gastric intrinsic factor

Pernicious anaemia  
Gastrectomy

Intestinal malabsorption

Ileal resection/Crohn's disease  
Stagnant loop syndrome  
Tropical sprue  
Fish tapeworm

Dietary deficiency

Congenital malabsorption  
Vegans

#### Folate deficiency

Dietary deficiency  
Malabsorption

Coeliac disease

Tropical sprue  
Small bowel disease resection

Increased requirement

Pregnancy  
Haemolytic anaemia  
Myeloproliferative / malignant / inflammatory disorders

#### Other causes

Drug induced suppression  
of DNA synthesis

Folate antagonists  
Metabolic inhibitors  
Nitrous oxide (prolonged use)

Inborn errors

Hereditary orotic aciduria

## HAEMOLYTIC ANAEMIA I – General features and inherited disorders

### GENERAL FEATURES OF HAEMOLYSIS

The term 'haemolytic anaemia' describes a group of anaemias of differing aetiology that are all characterised by abnormal destruction of red cells. The hallmark of these disorders is reduced life span of the red cells rather than underproduction by the bone marrow.

In classification of the haemolytic anaemias there are three main considerations:

The mode of acquisition of the disease: is it an inherited disorder or a disorder acquired in later life?

The location of the abnormality: is the abnormality within the red cell (intrinsic) or outside it (extrinsic)?

The site of red cell destruction: red cells may be prematurely destroyed in the blood stream (intravascular haemolysis) or outside it in the spleen, and liver (extravascular haemolysis).

The simple classification in Table 1 relies upon division of the main clinical disorders into inherited and acquired types. In general, it can be seen that inherited disorders are intrinsic to the red cell and acquired disorders extrinsic. The inherited disorders can be subdivided depending on the site of the defect within the cell - in the membrane, in haemoglobin, or in metabolic pathways. Acquired disorders (discussed in the next section) are broadly divided depending on whether the aetiology has an immune basis.

### DIAGNOSIS OF A HAEMOLYTIC ANAEMIA

Recognition of the general clinical and laboratory features of haemolysis usually precedes diagnosis of a particular clinical syndrome. Where haemolysis leads to significant anaemia the resultant symptoms are as for other causes of anaemia. However, the increased red cell breakdown of the haemolytic anaemias causes an additional set of problems. Accelerated catabolism of haemoglobin releases increased amounts of bilirubin into the plasma such that patients may present with jaundice. Where the spleen is a major site of red cell destruction there may be palpable splenomegaly. Severe prolonged haemolytic anaemia in childhood can lead to expansion of the marrow cavity and associated skeletal abnormalities including frontal bossing of the skull.

Table 1 Classification of the haemolytic anaemias

#### Inherited disorders

Red cell membrane

Hereditary spherocytosis and hereditary elliptocytosis

Haemoglobin

Thalassaemia syndromes and sickling disorders

Metabolic pathways

Glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency

#### Acquired disorders

Immune

Warm and cold autoimmune haemolytic anaemia

Isoimmune

Rhesus or ABO incompatibility (e.g. haemolytic disease of newborn, haemolytic transfusion reaction)

Non-immune and trauma

Valve prostheses, microangiopathy, infection, drugs or chemicals, hypersplenism

Initial laboratory investigations of haemolysis will include an automated blood count, a blood film and a reticulocyte count. The blood count will show low haemoglobin. Many cases of haemolysis have 'normochromic normocytic' red cell indices although some are moderately macrocytic. The latter observation is caused by the increased number of large immature red cells (reticulocytes) in the peripheral blood following a compensatory increase in red cell

production by the bone marrow. Reticulocytes have a characteristic blue tinge with Romanovsky stains and their presence in the film causes 'polychromasia'. A count of reticulocytes is performed either manually on a blood film stained with a supravital stain or by the automated cell counter.

Simple laboratory tests to detect increased breakdown of red cells are also useful indicators of haemolysis. In addition to moderately raised serum bilirubin (often 30-50 mol/l), there may be raised levels of urine urobilinogen and faecal stercobilinogen. Bilirubin itself is unconjugated and therefore does not appear in the urine. Haptoglobin, a glycoprotein bound to free haemoglobin in the plasma, is depleted in haemolysis. In intravascular haemolysis, haemoglobin and haemosidetin can be detected in the urine. Haemosiderin is present for several weeks after a haemolytic episode and is simply demonstrated by staining urine sediment for iron.

Examination of the bone marrow is not usually necessary in the work-up of haemolysis but, where performed, will show an increased number of immature erythroid cells. Formal demonstration of reduced red cell survival by tagging of cells with radioactive chromium ( $^{51}\text{Cr}$ ) and in vivo surface counting of radioactivity to identify the site of red cell destruction are other possible investigations infrequently performed in practice.

#### INHERITED DISORDERS DISORDERS OF THE RED CELL MEMBRANE

##### Hereditary spherocytosis

This autosomal dominant disease is the most common cause of inherited haemolytic disease in Northern Europeans. The defect in the red cell is a deficiency of spectrin, the major skeletal protein in the lattice-like structure which supports the membrane. Spectrin deficiency causes instability of the cell's lipid bilayer and a loss of surface area. In a blood film the red cells are spheroidal ('spherocytes') with a reduced diameter and more intense staining than normal red cells. These abnormal red cells are prone to premature destruction in the microvasculature of the spleen. The severity of haemolysis is variable and the disease may present at any age. Fluctuating levels of jaundice and palpable splenomegaly are common features. Occasionally, patients develop severe anaemia associated with the transient marrow suppression of a viral infection; this so-called 'aplastic crisis', which may intervene in any form of chronic haemolysis, is nearly always caused by the parvovirus. Prolonged haemolysis may lead to bilirubin gallstones.

Diagnosis is facilitated by the presence of a family history. The combination of general features of haemolysis and spherocytes in the blood is suggestive of hereditary spherocytosis but not diagnostic as spherocytes may also be seen in autoimmune haemolysis. The two haemolytic disorders are distinguished by the direct antiglobulin test which is negative in hereditary spherocytosis and nearly always positive in immune haemolysis.

Spherocytes have increased 'osmotic fragility' - they lyse at higher saline concentrations than normal red cells (Fig. 3). They also show an increased rate of haemolysis when incubated in their own plasma (the 'autohaemolysis test'). No treatment is required in patients with mild disease. In more serious cases the spleen is removed as this is the main site of destruction of the abnormal red cells.

##### Hereditary elliptocytosis

This disease has many similarities to hereditary spherocytosis but the cells are elliptical in shape and the clinical course is usually milder. Splenectomy helps in the rare severe cases. There are various subtypes with the most common structural change being a defective spectrin molecule.

#### ABNORMALITIES OF HAEMOGLOBIN

These disorders are referred to collectively as the 'haemoglobinopathies'. Thalassaemia and sickle cell syndromes are discussed in later sections.

#### ABNORMALITIES OF RED CELL METABOLISM

The red cell has metabolic pathways to generate energy and also to protect it from oxidant stress (Fig. 4). Loss of activity of key enzymes may lead to premature destruction; there are two common examples.

##### Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD is a necessary enzyme in the generation of reduced glutathione which protects the red cell from oxidant stress. Deficiency is sex-linked affecting males; female carriers show half normal G6PD levels. The disorder is most common in West Africa, Southern Europe, the Middle East and South-East Asia. Patients are usually asymptomatic until increased oxidant stress leads to a severe haemolytic anaemia, often with intravascular destruction of red cells. Common triggers include fava beans, drugs (many including antimalarials and analgesics) and infections. The disease can alternatively present as jaundice in the neonate. Diagnosis requires demonstration of the enzyme deficiency by direct assay - this should not be done during acute haemolysis as reticulocytes have higher enzyme levels than mature red cells and a 'false normal' level may result. Treatment is to stop any offending drug and to support the patient. Blood transfusion may be necessary.

##### Pyruvate kinase (PK) deficiency

In this autosomal recessive disorder patients lack an enzyme in the Embden-Meyerhof pathway. Red cells are unable to generate adequate ATP and become rigid. All general features of haemolysis can be present, but clinical symptoms are often surprisingly mild for the degree of anaemia as the block in metabolism leads to increased intracellular 2,3DPG levels facilitating release of oxygen by haemoglobin. Splenectomy may help in reducing transfusion requirements.

##### Haemolytic anaemia I - general features and inherited disorders

'Haemolytic anaemias' are caused by abnormal destruction of red cells.

Most inherited haemolytic disorders have a defect within the red cell whilst most acquired disorders have the defect outside the cell.

Haemolysis causes characteristic clinical features and laboratory abnormalities. It may be intra- or extravascular. Hereditary spherocytosis and hereditary elliptocytosis are haemolytic disorders caused by a deficiency in the red cell membrane.

Glucose-6-phosphate dehydrogenase and pyruvate kinase are key enzymes in red cell metabolism; inherited deficiency leads to haemolysis.

## HAEMOLYTIC ANAEMIA II – Acquired disorders

### AUTOIMMUNE HAEMOLYTIC ANAEMIAS

Autoimmune haemolytic anaemia (AIHA) is an example of an acquired form of haemolysis with a defect outside the red cell. The bone marrow produces structurally normal red cells and premature destruction is caused by the production of an aberrant autoantibody targeted against one or more antigens on the cell membrane. Once an antibody has attached itself to the red cell, the exact nature of the haemolysis is determined by the class of antibody and the density and distribution of surface antigens. IgM autoantibodies cause destruction by agglutination or by direct activation of serum complement. IgG class antibodies generally mediate destruction by binding of the Fc portion of the cell-bound immunoglobulin molecule by macrophages in the spleen and liver. The disparate behaviour of different types of autoantibody provides the explanation for a number of different clinical syndromes.

#### Classification

Table I shows a simple approach to the classification of autoimmune haemolytic anaemia. The disease can be divided into 'warm' and 'cold' types depending on whether the antibody reacts better with red cells at 37°C or 4°C. For each of these two basic types of autoimmune haemolysis there are a number of possible causes and these can be incorporated into the classification. A diagnosis of autoimmune haemolysis may precede diagnosis of the causative underlying disease.

#### Clinical presentation and management

**Warm autoimmune haemolytic anaemia** Warm AIHA (Figs 1 & 2) is the most common form of the disease. The red cells are coated with either IgG alone, IgG and complement, or complement alone. Premature destruction of these cells usually takes place in the reticuloendothelial system. Approximately half of all cases are idiopathic but in the other half there is an apparent underlying cause (Table 1). The autoantibody is usually non-specific with reactivity against basic membrane constituents present on virtually all red cells. Patients present with the clinical and laboratory features of haemolysis discussed in the last section. Splenomegaly is a frequent examination finding. The most characteristic laboratory abnormality in warm AIHA is a positive direct antiglobulin test (DAT) sometimes known as the Coombs' Test.

A major priority in management is the identification and treatment of any causative disorder. It is particularly important to stop an offending drug - commonly implicated agents include methyldopa and penicillin. Where the haemolysis itself requires treatment steroids are normally used (e.g. prednisolone 40-60 mg daily). In idiopathic AIHA most patients will respond to steroids with a significant rise in haemoglobin and diminished clinical symptoms. However, the disease is usually controlled rather than cured and relapses often occur when steroids are reduced in dose or stopped. Where refractoriness to steroids develops, splenectomy is usually indicated. Other immunosuppressive drugs (e.g. azathioprine) or even cytotoxic agents may be helpful in supplementing the immunosuppressive effect of prednisolone.

Table 1 Classification of the autoimmune haemolytic anaemias

#### Warm AIHA (usually IgG)

##### Primary (Idiopathic)

Secondary Lymphoproliferative disorders

Other neoplasms

Connective tissue disorders

Drugs

Infections

#### Cold AIHA (usually IgM)

##### Primary (Cold haemagglutinin disease)

Secondary Lymphoproliferative disorders

Infections (e.g. mycoplasma)

Paroxysmal cold haemoglobinuria

#### Cold autoimmune haemolytic anaemia

In cold AIHA the antibody is generally of IgM type with specificity for the I red cell antigen. It attaches best to red cells in the peripheral circulation where the blood temperature is lower. As is seen in Table I this kind of haemolysis can occur in the context of a monoclonal (i.e. malignant) proliferation of B-lymphocytes in the so called 'Idiopathic cold haemagglutinin syndrome' or in a variety of lymphomas. The other major cause is infection. The severity of haemolysis varies and agglutination (clumping) of red cells may cause circulatory problems such as acrocyanosis, Raynaud's phenomenon and ulceration. The haemolysis, where longstanding, is often worse in the winter. On occasion red cell destruction is intravascular due to direct lysis by activated complement. Where this occurs free haemoglobin is released into the plasma (haemoglobinuria) and may appear in the urine (haemoglobinuria) giving it a dark colour. Cold AIHA arising from infection is usually self-limiting. Where it is chronic the mainstay of treatment is keeping the patient warm, particularly in the extremities. In forms associated with lymphoproliferative disorders, cytotoxic drugs such as chlorambucil and cyclophosphamide can be helpful.

#### ISOIMMUNE HAEMOLYTIC ANAEMIA

Here alloantibodies (isoantibodies) cause haemolysis as a result of transfusion or transfer across the placenta. These antibodies are conventional antibodies specific for foreign antigens on incompatible red cells.

#### MICROANGIOPATHIC HAEMOLYTIC ANAEMIA

Collectively, microangiopathic haemolytic anaemia (MAHA) is one of the most frequent causes of haemolysis. The term describes intravascular destruction of red cells in the presence of an abnormal microcirculation. There are many causes of MAHA (Table 2) but common triggers are the presence of disseminated intravascular coagulation (DIC), abnormal platelet aggregation and vasculitis. Characteristic laboratory findings include red cell fragmentation in the blood film (Fig. 4) and the coagulation changes seen in DIC. Two specific syndromes merit brief description.

#### Thrombotic thrombocytopenic purpura (TTP)

This rare disorder often affects young adults and is characterised by MAHA, thrombocytopenia, fluctuating neurological symptoms, fever and renal failure. The pathology appears to be platelet clumping in small vessels. Mortality is high but patients can be rescued with intensive supportive care including plasma exchange with infusion of fresh frozen plasma (FFP).

#### OTHER ACQUIRED HAEMOLYTIC ANAEMIAS

Haemolysis associated with red cell fragmentation may also occur due to the mechanical effects of defective heart valves or in long distance runners who effectively stamp repeatedly on a hard surface ('march haemoglobinuria'). Certain drugs (e.g. dapsone and sulphasalazine) can cause oxidative intravascular haemolysis in normal people if taken in sufficient dosage. Many infections can cause haemolysis, either by direct invasion of red cells or via the circulatory changes already discussed. The anaemia of malaria often has a haemolytic component.

*Paroxysmal nocturnal haemoglobinuria* (PNH) (Fig. 5) is a rare example of acquired haemolysis caused by an intrinsic red cell defect. In this clonal disorder arising from a somatic mutation in a stem cell, the mature blood cells have faulty anchoring of several proteins to membrane glycoprophospholipids containing phosphatidylinositol. Clinical features are highly variable and include intravascular haemolysis, pancytopenia and recurrent thrombotic episodes, including portal vein thrombosis. There is coexistent marrow damage and PNH is often associated with aplastic anaemia and may even terminate in acute leukaemia. The traditional diagnostic test exploits the cell's unusual sensitivity to complement lysis (Ham Test) but the cell's characteristic lack of certain proteins (e.g. decay accelerating factor) can also be demonstrated by flow cytometry. Treatment is generally supportive with blood transfusion and anticoagulation as required. In young patients with severe disease allogeneic bone marrow transplantation can be curative.

Table 2 Causes of microangiopathic haemolytic anaemia

Haemolytic uraemic syndrome  
Thrombotic thrombocytopenic purpura  
Carcinomatosis  
Vasculitis  
Severe infections  
Pre-eclampsia  
Glomerulonephritis  
Malignant hypertension

#### Haemolytic anaemia II - acquired disorders

Autoimmune haemolytic anaemia (AIHA) can be divided into 'warm' and 'cold' types dependent on the temperature at which the antibody reacts optimally with red cells.

For each type of AIHA there are possible underlying causes which must be identified and treated.

The term 'microangiopathic haemolytic anaemia' (MAHA) describes the intravascular destruction of red cells in the presence of an abnormal microenvironment. Clinical syndromes associated with MAHA include haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura.

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare example of acquired haemolysis caused by an intrinsic red cell defect.

#### Haemolytic uraemic syndrome (HUS)

HUS mainly affects infants and children. The three main features are MAHA, renal failure and thrombocytopenia. The disease can occur as seasonal epidemics caused by *Escherichia coli* producing verotoxin; it is then preceded by bloody diarrhoea. Treatment is essentially supportive with dialysis for renal failure. Mortality range from 5 to 50%

## THE THALASSAEMIAS

The thalassaemias are a heterogeneous group of inherited disorders of haemoglobin synthesis. They are characterised by a reduction in the rate of synthesis of either alpha or beta chains and are classified accordingly (i.e.  $\alpha$ -thalassaemia,  $\beta$ -thalassaemia). The basic haematological abnormality in the thalassaemias is a hypochromic microcytic anaemia of variable severity. Unbalanced synthesis of  $\alpha$  and  $\beta$ -globin chains can damage red cells in two ways. Firstly, failure of  $\alpha$ - and  $\beta$ -chains to combine leads to diminished haemoglobinisation of red cells to levels incompatible with survival ('ineffective erythropoiesis'). Even those hypochromic cells released into the circulation transport oxygen poorly. The second mechanism for red cell damage is the aggregation of unmatched globin chains - the inclusion bodies lead to red cell destruction either in the marrow or in the spleen (i.e. haemolysis). In general terms, the clinical severity of any case of thalassaemia is proportionate to the degree of imbalance of  $\alpha$ - and  $\beta$ -globin chain synthesis.

Thalassaemias are amongst the most common inherited disorders. Cases occur sporadically in most populations but the highest thalassaemia gene frequency is in a broad geographical region extending from the Mediterranean through the Middle East and India to South-East Asia.

#### CLASSIFICATION

The classification illustrated in Table 1 is based on the mode of inheritance of thalassaemia. As the  $\alpha$ -globin chain gene is duplicated on each chromosome there may be total loss of  $\alpha$ -globin chain production (termed  $\alpha^0$  or  $-/-$  / haplotype) or partial loss of  $\alpha$  chain production resulting from loss of only one gene (termed  $\alpha^+$  or  $-/\alpha$  / haplotype).

The most important clinical syndromes are *haemoglobin (Hb)-Barts hydrops* syndrome ( $-/-/-$ ) which is incompatible with life and *Hb H Disease* ( $-/\alpha/-$ ). At the molecular level the majority of cases of  $\alpha$ -thalassaemia result from large deletions in the  $\alpha$ -globin gene complex; occasionally mutations can depress expression of the gene.

$\beta$ -thalassaemias are autosomal recessive disorders characterised by reduced ( $\beta^+$ ) or absent ( $\beta^0$ ) production of  $\beta$ -chains.

The heterozygous ('trait' or 'minor') form of the disease is usually symptomless whilst homozygosity is associated with the clinical disease  $\beta$ -thalassaemia 'major'. Homozygous mild  $\beta^+$ -thalassaemia may, however, lead to a less severe clinical syndrome termed 'thalassaemia intermedia'. The  $\beta$ -thalassaemias are very heterogeneous at the molecular level - the large majority of defects are single nucleotide substitutions affecting critical areas for the function of the  $\beta$ -globin gene.

Although precise classification of a thalassaemia syndrome may require sophisticated molecular analysis, diagnosis of the major clinical syndromes is normally possible from a careful consideration of the clinical features and simple laboratory tests. The latter must include a blood count and blood film, and haemoglobin electrophoresis with quantification of the different types of haemoglobin (i.e. HbA, HbA<sub>2</sub>, HbF).

Other structural Hb variants may coexist with thalassaemias giving rise to a wide range of clinical disorders. Only the more common thalassaemia syndromes are discussed here.

#### CLINICAL SYNDROMES

##### $\alpha$ -thalassaemias

###### **Hb-Barts hydrops syndrome ( $-/-/-$ )**

Here deletion of all four genes leads to complete absence of  $\alpha$ -chain synthesis. As  $\alpha$ -globin chain is needed for fetal haemoglobin (HbF) as well as adult haemoglobin (HbA) the disorder is incompatible with life and death occurs in utero (hydrops fetalis).

###### **HbH disease ( $-/\alpha/-$ )**

This disorder arises from deletion of three of the four  $\alpha$  globin genes and is found most commonly in South-East Asia. The clinical features are variable but there is often a moderate chronic haemolytic anaemia (Hb 70-110 g/l) with splenomegaly and sometimes hepatomegaly. The blood film shows hypochromic microcytic red cells with poikilocytosis, polychromasia and target cells. The HbH molecule is formed of unstable *tetramers* of unpaired  $\beta$  chains ( $\beta_4$ ). It is best detected by electrophoresis (at pH 6-7) but may be demonstrated as red cell inclusion bodies in

reticulocyte preparations. Special studies of globin chain synthesis show  $\alpha$  /  $\beta$  chain ratios varying between 0.2 and 0.4 (normally 1).

Table 1 Classification of thalassaemia

Type of thalassaemia	Heterozygote	Homozygote
$\alpha$ -thalassaemia*		
Thal. minor	Hydrops fetalis	
$\alpha$ , (- (X	Thal. minor	Thal. minor
$\beta$ -thalassaemia		
00Thal. minor	Thal. major	
PIthal. minor	Thal. major or	intermedia
Compound heterozygosity (4 u.)	leads to HbH disease.	

#### $\alpha$ -thalassaemia traits

Deletion of a single  $\alpha$ -globin chain leads only to a slight lowering of red cell mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) and even deletion of two genes usually only minimally lowers the haemoglobin with a raised red cell count and hypochromia and microcytosis. These carrier states can be difficult to identify in the routine laboratory as haemoglobin electrophoresis is normal. Occasional HbH bodies may be detected in reticulocyte preparations. Definitive diagnosis requires globin chain synthesis studies and/or DNA analysis.

#### $\beta$ -thalassaemias

##### $\beta$ -thalassaemia major

$\beta$ -thalassaemia major is characterised by an anaemia caused by  $\alpha$  chain excess leading to ineffective erythropoiesis and haemolysis. The anaemia is usually severe (Hb less than 70 g/l) and becomes apparent between 3-6 months when production of HbF declines. The child fails to thrive and develops hepatosplenomegaly. Compensatory expansion of the marrow space causes the characteristic thalassaemia facies with skull bossing and maxillary enlargement (Fig. 1a). The 'hair-on-end' radiological appearance of the skull (Fig. 1b) is due to expansion of bone marrow into cortical bone. If left untreated further complications can include repeated infections, bone fractures and leg ulcers.

Usually laboratory diagnosis is straightforward. Testing should precede blood transfusion. There is a severe hypochromic microcytic anaemia with a characteristic blood film (Fig. 2) and Hb electrophoresis demonstrates absence or near absence of HbA with small amounts of HbA<sub>2</sub> and the remainder HbF.

Recently, the objectives of management of thalassaemia major have subtly changed. With intense supportive therapy, increasing numbers of patients survive into adulthood and there is greater emphasis on the quality of life. Interventions are frequently directed at therapy related complications (e.g. iron overload, hepatitis C infection) and clinical problems which are not life threatening.

Blood transfusion remains the mainstay of management. Raising the haemoglobin concentration has two goals: to reduce tissue hypoxia and suppress endogenous haematopoiesis which is largely ineffective. Transfusion is generally given at 2-4 week intervals to maintain a mean haemoglobin level of around 120 g/l. Splenectomy can reduce the transfusion frequency. With such regular transfusion iron chelation is necessary to minimise iron overload. Without chelation, accumulation of iron damages the liver, endocrine organs and heart with death in the second or third decades. The most commonly used regimen is subcutaneous Desferrioxamine given for 5-7 days per week. Compliance may be problematic (especially in teenagers) but where good there is a considerably improved life expectancy. Oral iron chelators are available but their use to date has been limited by side-effects.

Unfortunately, patients with thalassaemia are also at risk for the infective complications of blood transfusion - hepatitis C is a potential cause of liver disease in many adults.

*Other aspects of management.* Folate should be prescribed wherever the diet is poor. Endocrine disturbances related to iron overload may require replacement therapy. Bone marrow transplantation is now a serious option in  $\beta$ -thalassaemia major. In 'best risk' patients the probability of survival exceeds 90%. Gene therapy may eventually be the definitive treatment.

#### Thalassaemia intermedia

Thalassaemia intermedia is a clinical syndrome which may result from a variety of genetic abnormalities (see Table 2). The clinical features are less severe than in  $\beta$ -thalassaemia major as the  $\alpha$  /  $\beta$ -globin chain imbalance is less pronounced possible mechanisms include mild  $\beta$ -thalassaemia alleles, the coexistence of  $\beta$ -thalassaemia and  $\alpha$ -thalassaemia, and enhancement of  $\gamma$ -chain production. Patients usually present later than is the case for  $\beta$ -thalassaemia major (often at 2-5 years), and have relatively high haemoglobin levels (80-100 g/l), moderate bone changes and normal growth. Patients do not require regular transfusion.

#### $\beta$ -thalassaemia trait (minor)

Heterozygotes for  $\beta^0$  or  $\beta^+$  are usually asymptomatic with hypochromic microcytic red cells and slightly reduced haemoglobin levels. The red cell count is elevated (greater than  $5.5 \times 10^9$  g/l). The key diagnostic feature is a raised HbA<sub>2</sub> level (4-7%). As in  $\alpha$ -thalassaemia trait the disorder is symptomless but not irrelevant. Firstly, it may be confused with iron deficiency leading to unnecessary investigations. Secondly, if both parents have  $\beta$ -thalassaemia trait there is a 25% chance of a child having  $\beta$ -thalassaemia major.

#### PRENATAL DIAGNOSIS

Prenatal diagnosis and carrier screening has led to a dramatic reduction in the incidence of thalassaemia in several Mediterranean populations. Prenatal detection is generally performed by molecular methods on amplified trophoblast DNA.

Table 2 Possible causes of thalassaemia intermedia

Mild defects of  $\beta$ -globin chain production, e.g. Homozygous mild  $\beta$ -thalassaemia  
Homozygosity or compound heterozygosity for severe  $\beta$ -thalassaemia with co-inheritance of  $\alpha$ -thalassaemia or genetic factors enhancing  $\gamma$  chain production.  
 $\beta$ -thalassaemia with co-inheritance of  $\beta$ -thalassaemia and  $\alpha$ -thalassaemia  
 $\beta$ -thalassaemia and hereditary persistence of fetal haemoglobin HbH disease

#### The thalassemias

The thalassemias are a heterogeneous group of inherited disorders where there is a reduction in the rate of synthesis of haemoglobin  $\alpha$  chains ( $\alpha$ -thalassaemia) or  $\beta$  chains ( $\beta$ -thalassaemia).

There may be both ineffective erythropoiesis and haemolysis. The basic haematological abnormality is a hypochromic microcytic anaemia.

There are several clinical syndromes. In general the severity is proportionate to the degree of imbalance of  $\alpha$  and  $\beta$  globin chains.

$\beta$ -thalassaemia major leads to severe anaemia requiring regular blood transfusion and iron chelation.

Thalassaemia trait is a symptomless clinical disorder which should not be confused with iron deficiency. Genetic counseling is required in selected cases.

## SICKLE CELL SYNDROMES

The sickle cell syndromes are a group of haemoglobinopathies which primarily affect the Afro-Caribbean population. The common feature of these diseases is inheritance of an abnormal haemoglobin  $\beta$  chain gene - the gene is designated  $\beta^S$ . Inheritance of two  $\beta^S$  genes leads to a serious disorder termed *sickle cell anaemia*. A similar syndrome can result from inheritance of the  $\beta^S$  gene with another abnormal  $\beta$  gene such as the haemoglobin C gene or  $\beta$  thalassaemia gene. Inheritance of the  $\beta^S$  gene with a normal  $\beta$  chain gene ( $\beta^A$ ) causes the innocuous sickle cell trait.

## PATHOPHYSIOLOGY

The abnormal  $\beta^S$  gene has a high, incidence in tropical and subtropical regions as the abnormal haemoglobin produced (HbS) gives some protection against falciparum malaria. HbS differs from normal haemoglobin (HbA) in that glutamic acid has been replaced by valine at the sixth amino acid from the N-terminus of the  $\beta$  globin chain. The clinical features of sickle cell anaemia arise from the propensity of red cells containing haemoglobin S to undergo 'sickling'. In the deoxygenated state the HbS molecules aggregate into long polymers which then align to form liquid crystals (tactoids). The red cell loses its normal deformability and becomes characteristically sickle shaped (Fig. 2). Damage to the membrane leads to increased rigidity and the ultimate sequestration of the red cell in the reticuloendothelial system causing haemolytic anaemia. The inflexible sickle cells also become lodged in the microcirculation causing stasis and obstruction.

## CLINICAL SYNDROMES

### SICKLE CELL ANAEMIA (HbSS)

This classical form of sickle cell syndrome is enormously variable in severity.

#### Haemolytic anaemia

The haemoglobin is generally in the range 60-100 g/l. Because HbS releases oxygen more readily than HbA, the symptoms of anaemia are often surprisingly mild. Intercurrent infection with parvovirus or folate deficiency can block erythropoiesis and cause a sudden fall in haemoglobin - the 'aplastic crisis'.

#### Vascular-occlusive crises

Acute, episodic, painful crises are a potentially disabling feature of sickle cell anaemia. They may be triggered by infection or cold. Patients complain of musculoskeletal pain which may be severe and require hospital admission. Hips, shoulders and vertebrae are most affected. Attacks are generally self-limiting but infarction of bone can occur and must be distinguished from salmonella osteomyelitis. Avascular necrosis of the femoral head is a crippling complication. Other organs are vulnerable to infarction; most serious is neurological damage which may manifest as seizures, transient ischaemic attacks (TIAS) and strokes. Vaso-occlusion in infancy is responsible for the 'hand-foot syndrome', a type of dactylitis damaging the small bones of hands and feet.

#### Sequestration crises

These arise from sickling and infarction within particular organs. Specific syndromes include 'acute chest syndrome' with occlusion of the pulmonary vasculature, 'girdle sequestration' caused by occlusion of the mesenteric blood supply, and hepatic and splenic sequestration.

#### Other complications

These are multiple, usually caused by vascular stasis and local ischaemia.

**Genitourinary.** Papillary necrosis with haematuria; loss of ability to concentrate urine; nephrotic syndrome; priapism.

**Skin.** Lower limb ulceration.

**Eyes.** Proliferative retinopathy; glaucoma.

**Hepatobiliary.** Liver damage; pigment gallstones.

#### Diagnosis

Diagnosis depends on the following:

#### Blood film appearance

**Screening tests for sickling.** The blood sample is deoxygenated (e.g. with sodium metabisulphite) to induce sickling.

#### Haemoglobin electrophoresis.

In sickle cell anaemia (HbSS) there is no HbA detectable.

#### Management

**General.** Patients need support in the community and easy access to centres experienced in the management of sickle cell anaemia. Prophylaxis is important. Thus, patients should avoid factors known to precipitate crises, take folate supplements (because of chronic haemolysis) and be prescribed penicillin and pneumococcal vaccine (because of hypoplasia caused by infarction). Infections require prompt treatment.

**Painful vascular-occlusive crises.** First line treatment is rest, increased fluids and adequate oral analgesia.

Constitutional upset or pain not relieved by oral analgesia necessitates hospital admission with continued rest, warmth, intravenous fluids and opiate analgesia.

**Blood transfusion.** Blood transfusion should be considered where severe anaemia (Hb less than 40 g/l) accompanies an acute crisis (haemolytic, aplastic or sequestration). Exchange transfusion can benefit patients with neurological symptoms, chest or girdle syndrome, priapism, or an unusually severe painful crisis. Longer term transfusion may be indicated where there are neurological complications, growth problems in childhood and, occasionally, to reduce the frequency of painful crises. The usual aim in these cases is to maintain the haemoglobin between 100 and 150 g/l with a HbS level of less than 25%.

**Pregnancy and surgery.** In pregnancy, women with problematic sickle cell anaemia (e.g. recent major complications or painful crises) or previous obstetric problems are likely to benefit from regular exchange transfusion. During surgery it is important to avoid hypoxia and dehydration. More severely affected patients can be given a course of transfusions preoperatively to reduce the HbS level.

#### Newer treatments

**Stimulating HbF production.** Increasing the level of fetal haemoglobin in red cells may reduce the severity of the disease. Recent studies of the antimetabolite hydroxyurea have been encouraging with a significant reduction in painful crises, major complications, blood transfusion and hospital admissions.

**Bone marrow transplantation.** This offers the possibility of a cure in selected patients but it will not be widely applicable until the toxicity is reduced.

**Gene therapy.** This has the potential to provide a cure without the risks of bone marrow transplantation.

#### Prognosis

With good management 80-90% of patients will survive to 20 years of age. The most common causes of death are infection in infancy, cerebrovascular accidents in adolescence and respiratory complications in adult life.

## DOUBLY HETEROZYGOUS SICKLING DISORDERS

Here patients inherit the  $\beta^S$  gene and another abnormal  $\beta$  gene - usually HbC or  $\beta$ -thalassaemia. HbSC disease is similar to HbSS but there is a tendency for fewer painful crises and a higher incidence of proliferative retinopathy and avascular necrosis. HbSp-thal is often severe with the entire range of sickling disabilities.

## SICKLE CELL TRAIT (HbAS)

Sickle cell trait normally causes no clinical problems as there is enough HbA in red cells (approximately 60%) to prevent sickling. However, haematuria occasionally occurs as a result of renal papillary necrosis and additional care is required during pregnancy and anaesthesia. Diagnosis is by a sickling test and Hb electrophoresis.

## COUNSELLING AND PRENATAL DIAGNOSIS

Genetic counseling is needed by those affected with either the homozygous disease, compound heterozygosity or the trait. Prenatal diagnosis is possible at 8 weeks from a chorionic villous sample. Various molecular methods are available for detecting the  $\beta^S$  gene but most laboratories currently rely on the polymerase chain reaction (PCR) for DNA amplification followed by direct detection by restriction enzyme analysis. The amplification refractory mutation system (ARMS) is used in ambiguous cases. Fetal blood analysis is still a useful backup where DNA analysis is not technically possible or where previously unstudied couples are referred late in pregnancy.

#### Sickle cell syndromes

The sickle cell syndromes are a group of haemoglobinopathies which primarily affect people of African origin.

Inheritance of two  $\beta^S$  genes leads to the serious clinical disorder, sickle cell anaemia (HbSS).

Clinical problems in sickle cell anaemia include chronic haemolytic anaemia, vascular-occlusive crises, sequestration crises and susceptibility to infection.

Routine management of sickle cell anaemia entails prophylactic measures, supportive care during vascular-occlusive crises and the selective use of blood transfusion.

Sickle cell trait (HBAS) is an innocuous clinical disorder but genetic counselling is often needed.

## ANAEMIA OF CHRONIC DISORDERS

Anaemia of chronic disorders (ACD) is a term used to describe a type of anaemia seen in a wide range of chronic inflammatory, infective and malignant diseases (Table 1). The anaemia often becomes apparent during the first few months of illness and then remains fairly constant (Fig. 1). It is rarely severe (haemoglobin  $\geq 90$  g/l; packed cell volume (PCV)  $\geq 0.30$ ) but there is some correlation with the intensity of the underlying illness. For instance, in infection the anaemia is often more marked where there is a persistent fever and in malignancy where there is widespread dissemination. Patients often suffer no symptoms from their anaemia or have only slight fatigue. The importance of this type of anaemia arises not from its severity but from its ubiquity. It is widely misunderstood (for such a common disorder) and ill patients are frequently subjected to excessive haematological investigation and unnecessary treatment with haematinics. The term ACD should not be used to describe other causes of anaemia such as haemolysis or bleeding which may also complicate chronic disorders. It has been argued that the designation ACD is inappropriate but other suggested terms appear even less satisfactory.

#### INCIDENCE

Because its causes are common, ACD is probably only second to iron deficiency as a cause of anaemia. It has been estimated to account for approximately half of all hospital cases of anaemia not explained by blood loss.

#### PATHOPHYSIOLOGY

The causation of the anaemia of chronic disorders has been extensively studied but questions remain. It appears to arise from a combination of decreased red cell production and shortened red cell survival.

The reason for shortened red cell survival is unclear. Patients with severe rheumatoid arthritis have mean red cell survivals of 80-90 days compared to 100-120 days in normal people. One hypothesis is that red cells are prematurely consumed due to overactivity of a reticuloendothelial system hypertrophied in the presence of chronic inflammation.

Table 1 Common causes of the anaemia of chronic disorders

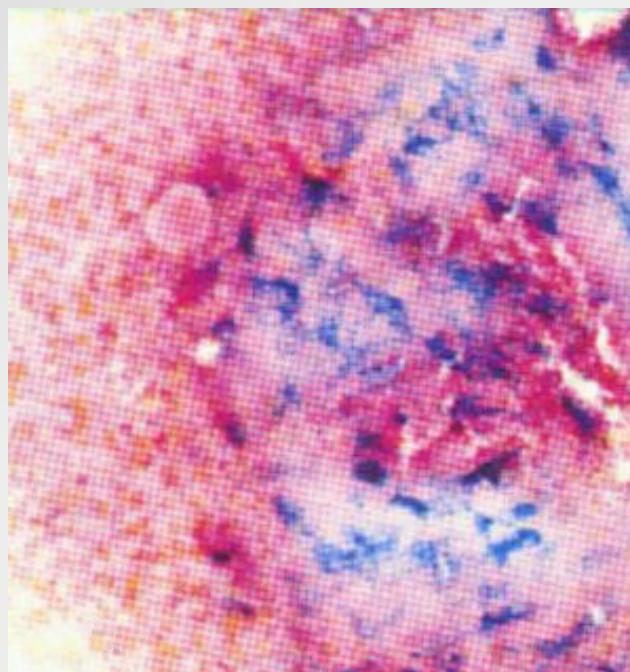
Malignancy
Rheumatoid arthritis
Various connective tissue disorders
Chronic infection
Extensive trauma

Probably reduced red cell survival is less important than red cell underproduction by the bone marrow. Abnormalities of iron metabolism are well documented in ACD. These include:

reduced iron absorption from the gastrointestinal tract  
decreased plasma iron concentration  
excessive retention of iron in reticuloendothelial cells (macrophages) with diminished release to erythroid cells.

The cause of these changes is contentious. It is possible that lactoferrin, a protein released from neutrophils during inflammation, binds serum iron and transfers it to macrophages thereby withholding it from red cell precursors. Another possibility is that increased levels of apoferritin, an acute phase reactant produced during inflammation, leads to the diversion of iron away from the bone marrow to be stored as ferritin. There could well be other factors impairing marrow function in ACD. Erythropoietin levels in some patients are lower than would be expected for the degree of anaemia. The response to erythropoietin is unimpaired, but there is no good evidence of an inhibitor to erythropoietin.

It has recently been suggested that many of the features of ACD can be explained by the release of interleukin-1, a cytokine produced by macrophages and present in inflammatory exudates. Its biological actions include:



ACD

generation of fever  
increased neutrophil production  
stimulation of the release of acute phase reactants from the liver  
lymphocyte proliferation.

Notably it also appears to promote release of lactoferrin from neutrophils and, at least experimentally, can cause a fall in serum iron concentration. Chronically increased production of interleukin-1, or other cytokines such as tumour necrosis factor (TNF), may be the mechanism for ACD.

#### DIAGNOSIS

Fig. 1. Bone marrow aspirate stained with Perls stain showing increased reticuloendothelial iron stores in

Most patients will have a documented chronic disorder and a moderate anaemia. On occasion the anaemia is a more dominant feature and the underlying cause is not immediately apparent. The anaemia is usually of normochromic nonnucleocytic type although it can be slightly hypochromic microcytic. The blood film appearance is often unremarkable but there may be changes 'reactive' to the underlying disorder such as a neutrophil leucocytosis, thrombocytosis and rouleaux formation. There is a reticulocytopenia. Serum iron concentration and total iron binding capacity (TIBC) are both low. The serum ferritin level is normal or high (as an acute phase reactant). In practice ACD is most commonly confused with mild iron deficiency anaemia, particularly if the MCV and MCH are reduced. However, the two forms of anaemia should be distinguishable as in uncomplicated iron deficiency the TIBC is elevated and the ferritin level is low (Table 2). Bone marrow examination is not routinely required in ACD but where performed will show normal or increased marrow iron stores with decreased marrow sideroblasts. It should be remembered that anaemia in a patient with a chronic medical disorder may be of multifactorial origin. It is important not to misdiagnose ACD as something else but equally it cannot be assumed that every patient with long-standing disease and a low haemoglobin has only ACD. In rheumatoid arthritis there is frequently co-existence of ACD and iron deficiency anaemia resulting from gastrointestinal bleeding due to drug therapy.

#### MANAGEMENT

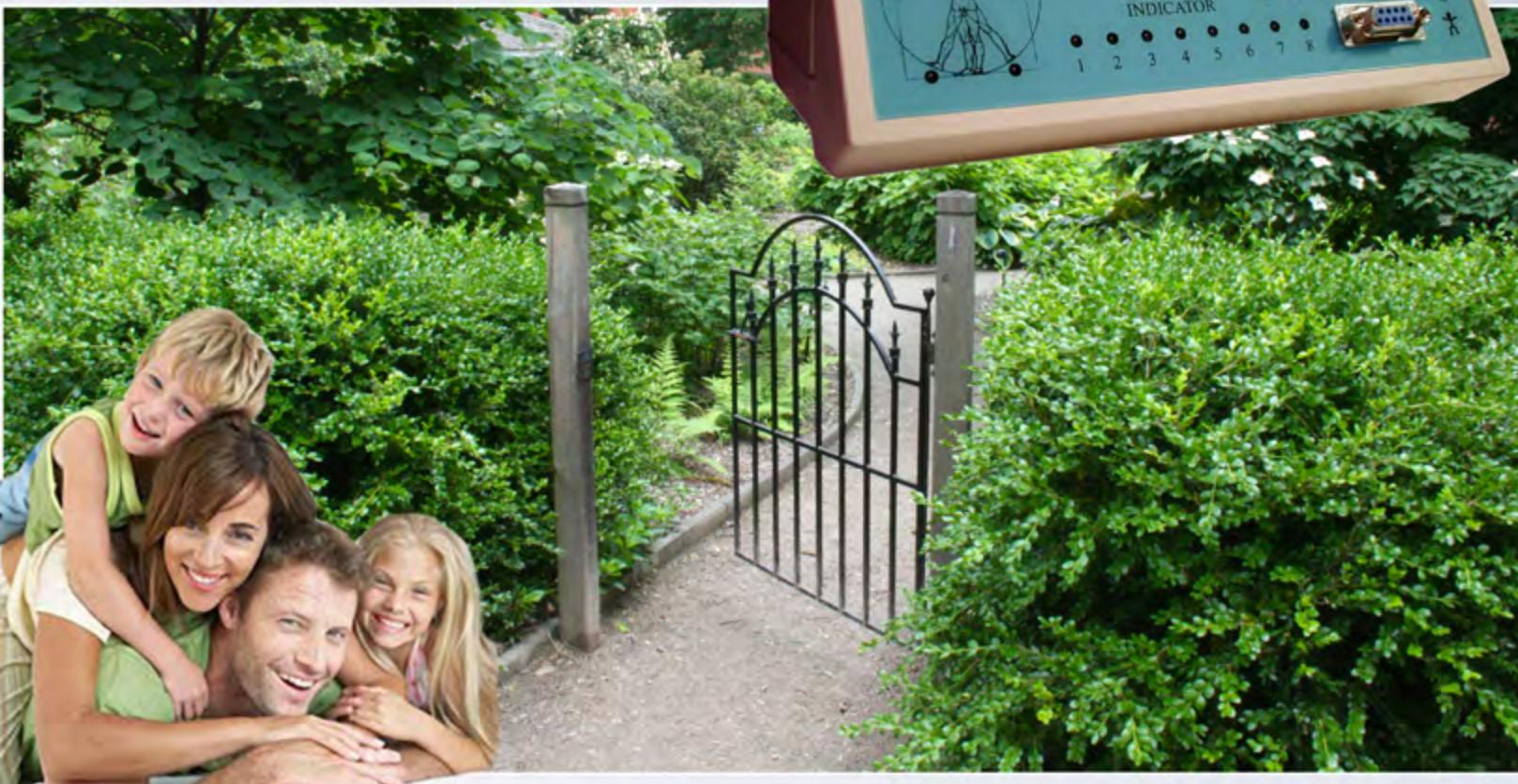
As the anaemia is usually non-severe and not progressive, the management is essentially that of the underlying disorder. Occasionally, patients cannot adequately compensate for the anaemia and require transfusion with plasma reduced red cells. In the absence of any proven deficiency replacement treatment with iron, vitamin B<sub>12</sub> or folate is worthless. Erythropoietin can be effective in relieving anaemia, particularly in rheumatoid arthritis and malignancy. However, there is not necessarily any symptomatic improvement. Erythropoietin is probably best reserved for patients with unusually severe ACD which is unlikely to respond rapidly to treatment of the chronic disorder.

#### Anaemia of chronic disorders (ACD)

ACD is seen in a wide range of chronic malignant, inflammatory and infective disorders. The pathogenesis of ACD is complex. There is a reduction in both red cell production and survival. Possible factors include abnormal iron metabolism, low erythropoietin levels and release of inflammatory cytokines. The anaemia is usually of normochromic, normocytic type, nonprogressive and is rarely severe. Treatment is that of the underlying disorder. Transfusion and erythropoietin may help in selected cases. In the absence of proven deficiency haematinic therapy is worthless.

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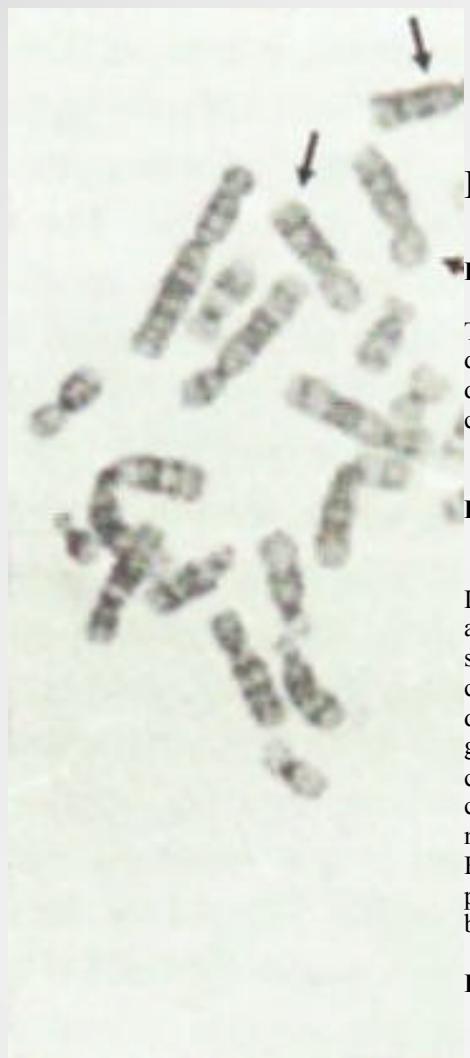
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## LEUKAEMIA

### INTRODUCTION

The leukaemias are a heterogeneous group of malignant blood disorders. In this introductory section general characteristics such as definitions, aetiology and classification are discussed. Each of the more common types of leukaemia is subsequently described in more detail.

### DEFINITION

Leukaemia is a type of cancer caused by the unregulated proliferation of a clone of immature blood cells derived from mutant haematopoietic stem cells. The malignant cells arise out of the arrest of normal blood cell maturation - they are effectively trapped at an early stage of differentiation. It is tempting to think of these leukaemic cells as fast-growing and aggressive. In fact, even in acute leukaemia the malignant cells cycle much more slowly than normal cells. If this was not the case, normal haematopoietic cells would not repopulate the bone marrow after the ablation that follows cytotoxic chemotherapy. However, leukaemic cells are indifferent to normal feedback signals and proliferate relentlessly, eventually squeezing out normal cells from the bone marrow and causing marrow failure and death.

Fig. 1 Trisomy 8 in acute myeloid leukaemia

### INCIDENCE

Leukaemia is not a rare disorder but it is less common than some malignancies of solid organs. There is a male preponderance in most types of leukaemia. Geographic variations exist; for instance, chronic lymphatic leukaemia is the most common form of leukaemia in the western world but is much less frequent in Japan, South America and Africa.

### AETIOLOGY

As for other malignancies the evolution of leukaemia is likely to be a multistep process. It is easiest to think about the aetiology in terms of acquired cytogenetic abnormalities and other predisposing factors.

#### Chromosomal abnormalities

Recent advances in cytogenetic analysis and particularly in molecular cytogenetic techniques have revealed various acquired chromosomal derangements which play a fundamental role in leukaemogenesis. There are a number of different types of possible chromosomal change.

#### Chromosomal Translocations

One chromosome breaks and donates a fragment to another chromosome which reciprocates by returning a fragment of its own. Such translocations can result in the movement of protooncogenes to new sites where they have the capacity to cause leukaemic transformations. The classical example of a translocation is the 'Philadelphia chromosome' which is found in 95% of cases of chronic myeloid leukaemia (CML) where breakages in chromosomes 9 and 22 result in the creation of a new fusion gene (bcr-abl) which encodes a novel protein with

intense tyrosine kinase activity. In a manner incompletely understood, this protein causes deregulated myeloid cell growth.

#### Chromosome deletions and additions

A chromosome may be completely or partly deleted, for example monosomy 7 in acute myeloid leukaemia (AML). Here a normal gene may be lost allowing expression of a recessive cancer gene. Conversely, an additional chromosome may be gained (e.g. Trisomy 8 in AML).

#### Point mutations

A change in the base sequence of certain oncogenes may predispose to leukaemia. The c-ras oncogene which encodes a protein vital in signal transduction is mutated in 50% of cases of AML.

#### Gene amplification

Certain proto-oncogenes may be amplified in leukaemia (e.g. C-MYC in AML). Particular chromosome changes are often associated with specific types of leukaemia (e.g. the Philadelphia chromosome in CML). However, few abnormalities are entirely specific - the Philadelphia chromosome can be found in cases of acute leukaemia. It should also be noted that not all cases of leukaemia have a detectable cytogenetic abnormality. The incidence of abnormality is partly dependent on the laboratory expertise available.

Table 1 Factors predisposing to leukaemia

#### Radiation exposure

Previous chemotherapy (particularly alkylating agents)  
Occupational chemical exposure (e.g. benzene)  
Some genetically determined disorders (e.g. Down's syndrome)  
Viral infection (only HTLV-1 proven as a causative factor)  
Other possible (e.g. cigarette smoking)

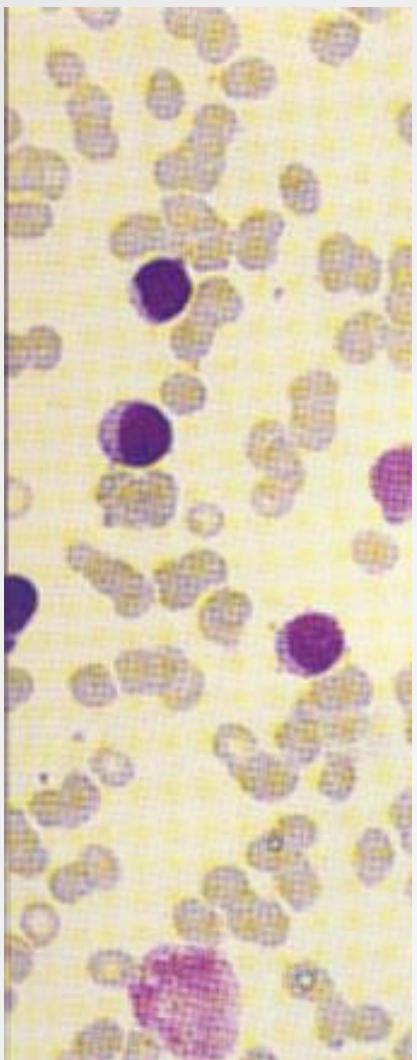
#### Predisposing factors

In a small subpopulation of leukaemic patients there is another obvious predisposing factor - the more common of these are listed in Table 1.

There is no doubt that higher doses of radiation can cause leukaemia. The incidence of acute leukaemia and chronic myeloid leukaemia increases with dose exposure for all age groups. Classic studies have included people exposed to the atomic bombs in Japan and patients receiving radiotherapy for ankylosing spondylitis in the middle years of this century. Of greater current concern is the estimate that approximately 1% of all leukaemias may be attributed to diagnostic radiation. The risk of leukaemia increases with an increasing number of X-rays but it is difficult to recommend a safe upper limit. Paternal preconception X-ray exposure has been associated with an increased incidence of acute leukaemia in offspring.

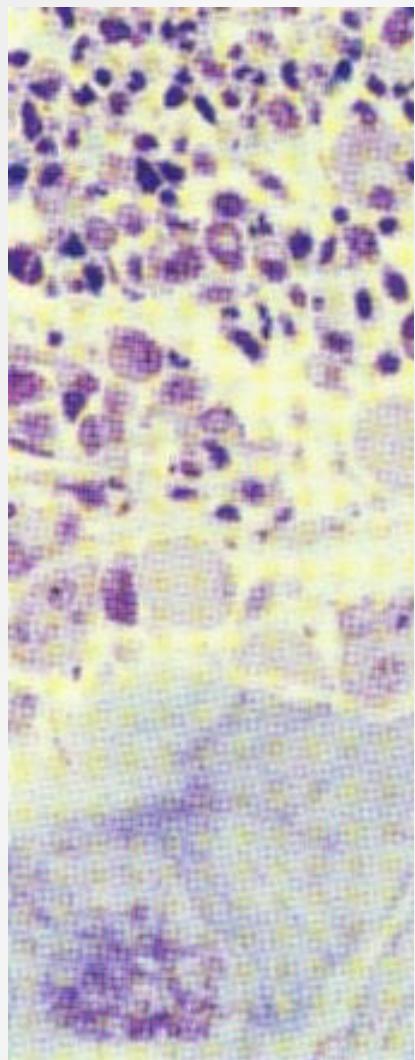
Cytotoxic chemotherapy, particularly with alkylating agents, leads to an increased risk of leukaemia. The risk appears to be greatest in older patients also treated with radiotherapy. The best established occupational leukaemogenic exposure is undoubtedly to benzene. A number of genetically determined diseases also predispose to leukaemia. Here the liability to leukaemia is probably caused by factors such as increased chromosomal breakage (e.g. Fanconi's anaemia) and immunosuppression (e.g. ataxia telangiectasia).

Viruses are known to be the main cause of leukaemia in many animals but in man the only well-proven association is of the HTLV-1 virus with the rare disorder T-cell leukaemia lymphoma.



**Fig. 2**

**Fig. 2** Peripheral blood film in a young woman with acute myeloid leukaemia.



**Fig. 3**

**Fig. 3** Bone marrow trephine appearance in human T-cell leukaemia lymphoma.

## CLASSIFICATION

In such a potentially complex group of disorders it is helpful to use a relatively simple classification. The leukaemias can most broadly be divided into acute and chronic types depending on their clinical course. The classification illustrated here further divides leukaemias into their cell of origin (i.e. myeloid or lymphoid) and refers to the microscopic appearance (morphology) of the leukaemic cells. The standard classification of the acute leukaemias is that of the FAB group - the abbreviation being for the French, American and British nationalities of the terminologists.

In the following pages are discussed acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia and chronic lymphatic leukaemia. Together these four diseases constitute the overwhelming majority of leukaemias in clinical practice. A few rarer types of leukaemia are discussed separately.

**Table 2 Classification of leukaemia**

### **Acute leukaemia** *Acute myeloid leukaemia*

Subdivided into eight types designated FAB M0-7 depending on the morphology of leukaemic cells (e.g. FAB M5 is acute monocytic leukaemia)

**Acute lymphoblastic leukaemia** Subdivided either on the basis of morphology (FAB L1, L2 and L3) or on the basis of leukaemic cell expression of surface antigens. This latter 'immunologic' classification includes common, null, B and T types.

### **Chronic leukaemia**

*Chronic myeloid leukaemia*  
*Chronic lymphatic leukaemia*  
Hairy cell leukaemia  
Prolymphocytic leukaemia  
T-cell leukaemia lymphoma

### **Other types**

#### **Leukaemia: introduction**

Leukaemia is a type of cancer caused by the unregulated proliferation of a clone of immature blood cells. Leukaemia is a heterogeneous group of clinical disorders classified on the basis of their clinical course (acute or chronic) and their cell of origin (myeloid or lymphoid). The aetiology of leukaemia is likely to be multifactorial with known predisposing factors such as radiation exposure present in only a minority of cases. Acquired chromosomal abnormalities play a fundamental role in leukaemogenesis with certain changes associated with particular types of leukaemia.



## ACUTE MYELOID LEUKAEMIA

### INTRODUCTION

Acute myeloid leukaemia (AML) arises out of the malignant transformation of a myeloid precursor cell. Usually this occurs at a very early stage of myeloid development, although acute promyelocytic leukaemia, a subtype of AML, involves proliferation of a more mature cell. AML is rare in childhood and the incidence increases with age. Cases may occur *de novo* or secondary to well-defined predisposing factors such as previous chemotherapy or a myelodysplastic syndrome - such cases are referred to as, secondary AML.

**Fig. 1** Gum infiltration in acute monocytic leukaemia.

### CLASSIFICATION

The classification of AML is based upon the appearance of the leukaemic cells in a bone marrow aspirate. The French American-British (FAB) group have described eight different variants of AML. An experienced haematologist can often identify the subtype on microscopy, but certain types (e.g. AML M0) routinely require other tests to establish a *fin-n* diagnosis. In all cases, but particularly in the elderly, the presence of dysplastic features suggests evolution from a myelodysplastic syndrome. Where dysplasia is prominent, the disease is arbitrarily termed leukaen-fia when the leukaemia cell ('blast') number in the marrow equals or exceeds 30% of all nucleated cells. Occasional cases of acute leukaemia show megakaryocytic or erythroid differentiation but are included in the AML classification.

### CLINICAL FEATURES

In practice there is little uniformity in presentation. Some patients are remarkably asymptomatic whilst others are seriously ill.

#### General

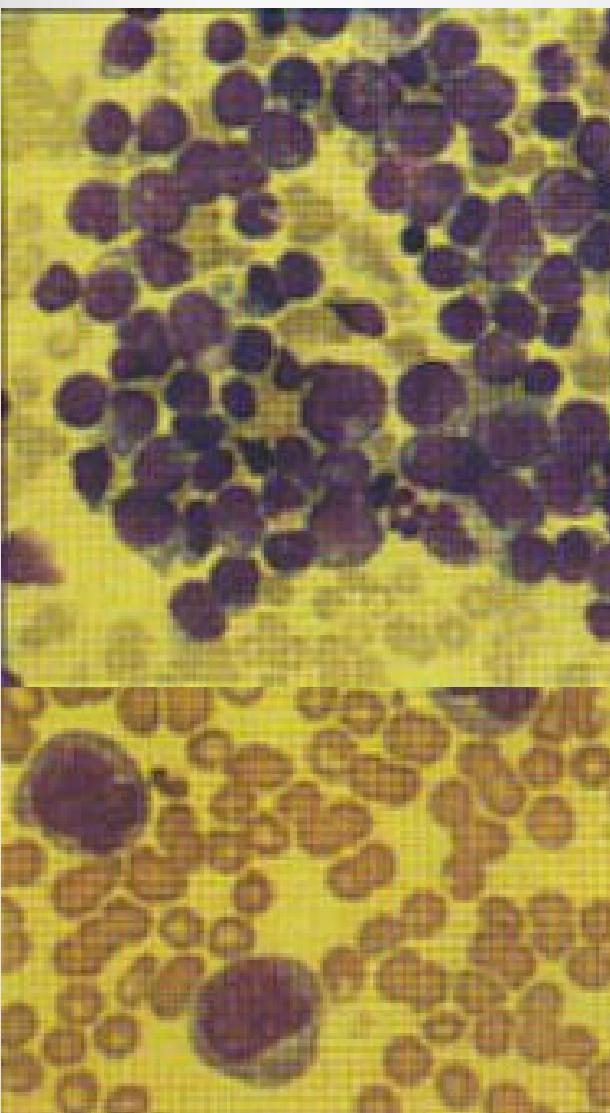
Bone marrow infiltration by leukaemic blast cells usually leads to anaemia, neutropenia and thrombocytopenia. Thus, patients often have symptoms of anaemia, infection and haemorrhage. Tissue infiltration by leukaemic cells and clotting problems may occur in any case of AML but are characteristic of specific subtypes.

**Table 1** Classification of acute myeloid leukaemia

Type	Description
M0	Undifferentiated
M1	Without maturation
M2	With maturation
M3	Promyelocytic
M4	Myelomonocytic
M5	Monocytic
M6	Erythroleukaemia
M7	Megakaryoblastic

#### Particular subtypes

**AML FAB M3 (acute promyelocytic leukaemia).** AML always requires prompt attention but this subtype is a true medical emergency. Patients are likely to develop disseminated intravascular coagulation (DIC) with disordered clotting tests and a high risk of spontaneous bleeding into vital organs.



**AML FAB M5 (acute monocytic leukaemia).** This subtype has a particular pro-

**AML FAB M7 (acute megakaryoblastic leukaemia).** This type is often associated with pancytopenia and marrow fibrosis. It is sometimes called 'acute myelofibrosis'.

### DIAGNOSIS

Diagnosis depends on a logical sequence of tests.

- Blood count.** The white cell count (WCC) is usually elevated (up to  $200 \times 10^9/l$ ) but may be normal or low. There is often anaemia and thrombocytopenia.
- Blood film.** Usually there are leukaemic blast cells although occasionally these are absent. There may be dysplastic changes in other cells.

- Bone marrow aspirate and trephine.** The bone marrow is infiltrated by leukaemic blast cells. In more immature forms of AML (e.g. M0, M1), differentiation from acute lymphoblastic leukaemia (ALL) can be difficult.

- Cytchemistry.** Special stains are used on bone marrow and blood smears to help differentiate myeloid and lymphoid blast cells. In AML there is positivity with Sudan black and myeloperoxidase - these stains are negative in ALL. AML with monocytic features (i.e. M4 or M5) will stain positively with a non-specific esterase stain.

- Immunophenotyping.** The basic concept has been described. In AML the leukaemic cells have characteristic myeloid antigens on the cell surface which have been allotted 'cluster differentiation' (CD) numbers to ease identification. Thus CD 13 and 33 are general myeloid markers and usually positive. CD 11 and 14

expression indicate monocytic differentiation, whilst CD 34 indicates a particularly immature cell of origin.

- Cytogenetics.** A bone marrow sample is sent for analysis. Chromosomal abnormalities in the leukaemic cells may suggest a particular subtype and also give prognostic information.

- Molecular biology.** As the molecular abnormalities in AML are better understood the role of molecular biology techniques will expand. Currently the best characterised abnormality is the t(15, 17) translocation of acute promyelocytic leukaemia in which the retinoic acid receptor (RAR) gene on chromosome 17 is brought into alignment with the PML gene on chromosome 15.

### MANAGEMENT

#### Supportive care

This includes red cell transfusion for anaemia, platelet concentrates for thrombocytopenia and broad spectrum intravenous antibiotics for infection. An indwelling central venous catheter facilitates support during and after chemotherapy.

#### Chemotherapy and bone marrow transplantation

The first objective of treatment with cytotoxic drugs is to achieve a 'complete remission' (CR) - defined as less than 5% blast cells in a normocellular bone marrow. Initial cytotoxic drug treatment is termed 'induction'. A CR is followed by a second sequence of drugs termed 'consolidation'. Induction and consolidation take at least several

months, but longer term 'maintenance' treatment is rarely given in AML. Regimens are ever changing but drugs commonly used in induction are combinations of an anthracycline (e.g. Daunorubicin), cytosine arabinoside and 6-thioguanine. Other agents such as amsacrine or etoposide may be included in induction or added to consolidation regimens. Acute promyelocytic leukaemia is treated with the differentiating agent all trans retinoic acid (ATRA) which reduces the risk of early death from bleeding and may improve long-term survival compared with chemotherapy alone. Autologous bone marrow transplantation (BMT) can be used to intensify chemotherapy but the benefit has proved difficult to quantify. The precise role of allogeneic BMT is not clearcut - most clinicians would transplant in a younger patient (less than 40 years) in first CR where an HLA identical sibling was available.

**Fig. 2** Bone marrow appearance in different subtypes of AML. **a:** the leukaemic blast cell shows some granulocytic differentiation, **b:** myelomonocytic

**Table 2 Common cytogenetic abnormalities in AML**

Abnormality	Associated subtype	Prognosis*
t (8,21)	AML M2	Good
t (15,17)	AML M3	Good
inv 16	AML M4	Good
5 and 7 (various)	Secondary AML	Poor

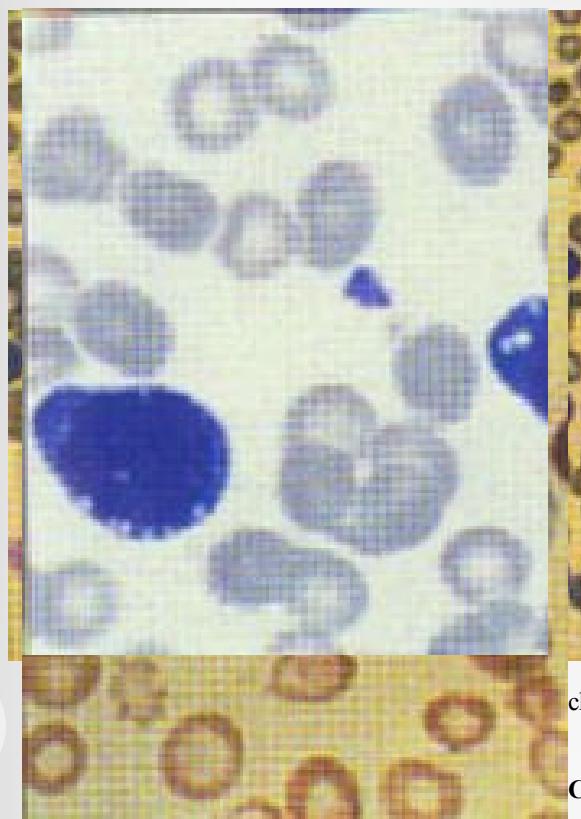
Compared with AML with normal karyotype

### PROGNOSIS

Approximately 80-90% of younger patients with AML will achieve a CR with conventional chemotherapy. Unfortunately, most will relapse and 'cure' rates are around 30%. Allogeneic BMT may increase this figure to around 50% but is generally limited to young patients with a matched sibling donor. Older patients tolerate chemotherapy less well and CR and cure rates are much lower. Indeed, it may be kinder not to use chemotherapy in some elderly patients. In children, intensive chemotherapy gives 3-year survival rates of around 50%. Apart from advancing age, other poor prognostic factors include secondary AML, certain cytogenetic abnormalities (Table 2), central nervous system disease and a high presentation WCC.

### Acute myeloid leukaemia

AML arises out of the malignant transformation of a myeloid precursor cell. The disease is divided into eight subtypes (FAB MO-M7) determined by the malignant cells' morphology and immunophenotype. Symptoms result from anaemia, neutropenia and thrombocytopenia. Tissue infiltration often complicates the monocytic subtype (FAB M5) and coagulopathy the promyelocytic subtype (FAB M3). Chemotherapy leads to CR rates of 80-90% in younger patients but cure rates are lower, around 30%. Bone marrow transplantation can cure around 50% of selected patients. Older patients tolerate chemotherapy less well and cure is rarely achievable.



## ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia (ALL) is a clonal malignancy of lymphoid precursor cells. In approximately 80% of cases the malignant cells are primitive precursors of B lymphocytes and the remainder are T-cell leukaemias. The abnormal cell may arise at various stages of early lymphocyte differentiation.

ALL has a peak incidence in childhood with a gradual rise in incidence in later years. The disease has distinct characteristics in children and adults. Childhood ALL is often curable by chemotherapy whereas cure is elusive in adult ALL. This is probably because most cases of adult disease involve a more immature precursor cell (a multipotential stem cell) whereas the malignant cell of childhood ALL is a committed lymphoid precursor cell.

### CLASSIFICATION

Both morphological and immunological features are used in classification. The French-American-British (FAB) morphological classification is based on characteristics of the blast cells including cell size, nuclear-cytoplasmic ratio, number and size of nucleoli and the degree of cytoplasmic basophilia. Most childhood cases have L1 morphology whereas the L2 type most often occurs in adults.

Immunological subtypes of ALL include common, null, B and T phenotypes. Definition depends on the presence or absence of various cell surface antigens. The most frequent immunological subtype is common ALL. Null cell ALL is thought to arise from a very primitive cell and is more common in adults. B-ALL is a rare disease with L3 morphology which often behaves as an aggressive lymphoma (Burkitt's variant').

In a significant minority of cases ALL the blasts express cell surface antigens usually found on myeloid cells (e.g. CD13, CD33) and a few of these are probably true 'biphenotypic' leukaemias with clinical presentations typical of neither ALL or AML.

**Fig. 1 a, b, c** Morphology of ALL blast cells, L1 type, L2 type, L3 type

### CLINICAL FEATURES

These can be very variable. Accumulation of malignant lymphoblasts in the marrow leads to a scarcity of normal cells in the peripheral blood and symptoms may include those associated with anaemia, infection and haemorrhage. Other common complaints are anorexia and back or joint pain. T-cell ALL is associated with a large mediastinal nodal mass and pleural effusions which result in dyspnoea. Central nervous system (CNS) involvement is more often seen in ALL than in AML and patients can present with symptoms of raised intracranial pressure (headache, vomiting) or cranial nerve palsies (particularly VI and VII). Examination findings may include pallor, haemorrhage into the skin and mucosae, lymphadenopathy and moderate hepatosplenomegaly. In males the testes can be involved and should be routinely examined.

**Table 1 Classification of ALL**  
**Morphological classification\***

- L1 Small uniform blast cells with scanty cytoplasm
- L2 Large heterogeneous blast cells with nucleoli and low nuclear cytoplasmic ratio
- L3 Basophilic vacuolated blast cells

## Immunological classification

Precursor B-ALL  
- common ALL  
- null ALL  
- pre-B ALL  
T-ALL  
B-ALL

## DIAGNOSIS

### 1. Blood count

The white cell count may be raised, normal or low. Only 20% have white cell counts greater than  $50 \times 10^9/l$ . Anaemia and thrombocytopenia are common.

### 2. Blood film

The proportion of blast cells in the white cell count varies from 0 to 100%. In some cases there is a leucoerythroblastic picture and teardrop shaped red cells.

### 3. Bone marrow aspirate and trephine

This is essential to confirm the diagnosis and for classification. A trephine biopsy is particularly helpful where the marrow is difficult to aspirate.

### 4. Cytochemistry

Stains which classically show positivity in AML-Sudan black and myeloperoxidase-are negative in ALL. Cytochemistry is useful in distinguishing precursor B and B-ALL from T-ALL. Reactivity with the acid phosphatase stain is seen in malignant T lymphocytes but not in B cells which may show periodic acid Schiff (PAS) block positivity.

### 5. Immunophenotyping

This technique plays a key role in classification. Useful reagents for establishing the diagnosis and identifying the immunological subtype include antibodies to CD19 and CD22 (found in most B-lineage ALLs), CD10 (the 'common ALL antigen'), CD3 and CD7 (found in T-lineage ALLs). CD3 may be detected in the cytoplasm but not on the membrane and there are other helpful cytoplasmic markers.

The accumulation of heavy chains in the cytoplasm is characteristic of a subtype of B-lineage ALL termed pre-B. The intracellular marker, terminal deoxynucleotidyl transferase (TdT), is found in most B- and T-lineage ALLs but can also be found in AML.

### 6. Cytogenetics

Cytogenetic analysis is doubly useful as structural abnormalities correlate with particular subtypes of ALL and both structural and numerical abnormalities give prognostic information. Varying patterns of cytogenetic abnormality may partly explain the different prognosis in children and adults. The Philadelphia chromosome, regarded as a marker of 'incurability' by chemotherapy, is found in 20-30% of adult cases but in only 5% of children.

### 7. Molecular biology

In B-lineage ALL, rearrangement of the immunoglobulin genes is frozen and monoclonal; the same is true of the T-cell antigen receptor genes in T-ALL. However, interpretation requires caution as cross-lineage rearrangements occur in around 10% of cases and immunoglobulin and T-cell receptor rearrangements may even be found in AML. Where routine cytogenetic analysis fails, molecular techniques should be used to search for the bcr-abl rearrangement as this predicts a poor response to chemotherapy.

## MANAGEMENT AND OUTCOME

### General principles

Patients with ALL require supportive care. Chemotherapy is the mainstay of treatment. Drug schedules vary but remission induction classically relies on three agents: vincristine, prednisolone and L-asparaginase. The

anthracycline daunorubicin may be included in the induction regimen and other drugs, notably methotrexate, etoposide and cytosine arabinoside, then added in 'intensification' and 'consolidation'. The rationale for early intensification of treatment is to reduce the leukaemic cell population quickly and reduce the likelihood of drug resistance. Therapy is completed with a period of 'maintenance' using methotrexate and mercaptopurine. The higher risk of CNS disease in ALL (than in AML) necessitates prophylactic treatment to prevent CNS relapse. The usual method is a combination of intrathecal injections of methotrexate and cranial irradiation. The ultimate choice of management is influenced by a number of prognostic factors. Where clinical and laboratory features predict a poor response to chemotherapy alone, transplantation (BMT) are considered. Of all the prognostic more intensive treatments such as allogeneic bone marrow indices the most influential is age.

### ALL in children

The majority of children are curable with current chemotherapy regimens. The standard strategy is intensive induction therapy, CNS prophylaxis, and maintenance treatment for 2 years. In children receiving the most intensive protocols, 5-year disease free survivals of 70% have been achieved. Autologous and allogeneic BMT is best reserved for relapse after chemotherapy or for cases with poor prognostic features at presentation. With improved cure rates the long-term side-effects of the drugs, including endocrine problems, secondary leukaemia and cardiotoxicity, are becoming increasingly relevant. Wherever feasible, the use of agents with the safest profiles is desirable.

### ALL in adults

The majority of adult patients are not curable with chemotherapy alone and only 20% will become long-term survivors. Most chemocurable patients are aged between 15 and 20 years with other good prognostic features. This 'good risk' subgroup resembles childhood ALL and chemotherapy alone is a reasonable initial policy. For the remainder of adults the hope of cure is likely to depend on even more intensive therapy either with autologous or allogeneic BMT. Allogeneic BMT from an HLA matched family donor performed in first remission gives long-term survival of around 40%. BMT using an unrelated HLA 'matched' donor is more risky but can be successful. Optimum management of adult ALL has yet to be defined and there is a need for careful consideration of all the known prognostic factors in each case. The choice of drugs for treating relapsed patients is arbitrary but the increasing availability of laboratory techniques for detecting drug resistance may allow more rational selection in the future. Elderly patients (over 60 years) tolerate chemotherapy less well and cure rates are very low. In these cases it is often better to concentrate on palliation of symptoms and provision of a short period of good quality life rather than undertaking aggressive chemotherapy with a negligible chance of success.

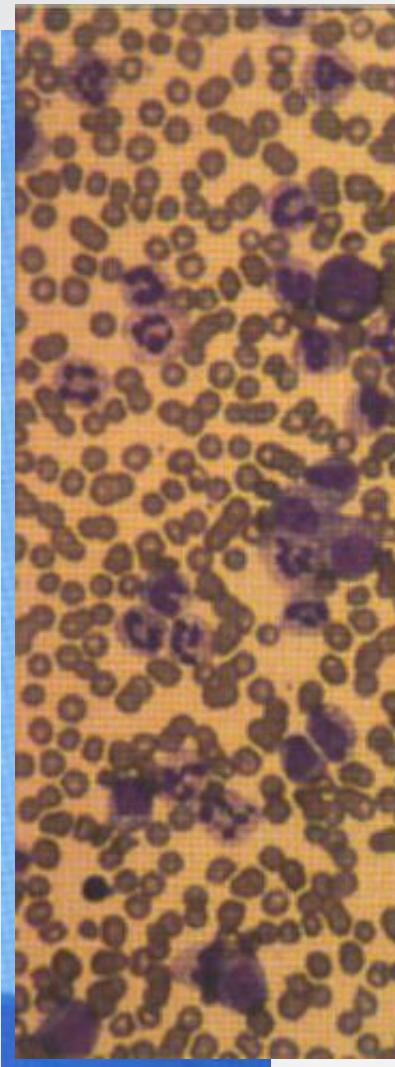
### Acute lymphoblastic leukaemia

ALL is a clonal malignancy of lymphoid precursor cells.

There is a peak incidence in childhood and a gradual rise in later years.

Accumulation of lymphoblasts in the bone marrow often leads to anaemia, infection and haemorrhage. CNS involvement is more common than in acute myeloid leukaemia.

The majority of children are curable with standard chemotherapy regimens and CNS prophylaxis. In adults, cure by chemotherapy alone is much less frequent. Autologous or allogeneic bone marrow transplantation may be considered in 'poor risk' cases.



## CHRONIC MYELOID LEUKAEMIA

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder which is thought to result from an acquired genetic change in a pluripotential stem cell. The disease is characterised by a gross overproduction of neutrophils and their precursors. It is unusual in having three clinical phases. A relatively benign 'chronic phase' is followed by an ominous 'accelerated phase' and, finally, an almost invariably fatal acute leukaemic phase termed 'blast crisis'.

The annual incidence of CML is around one per 100 000 with presentation most common in the fifth and sixth decades of life. The diagnosis is increasingly made in asymptomatic patients having routine blood tests.

### PATHOGENESIS

The hallmark of CML cells is the presence of a Philadelphia (Ph) chromosome - the (9, 22)(q34, q11) chromosomal translocation. Over 95% of classical CML cases are Ph positive. The Ph translocation causes the fusion of the c-abl proto-oncogene from chromosome 9 to the interrupted end of the breakpoint cluster region (bcr) of chromosome 22. The normal functions of the abl and bcr genes are unclear. The chimeric bcr-abl gene created on the Ph chromosome (22q-) encodes a protein with considerably greater tyrosine kinase activity than the normal counterpart. This protein presumably acts as an oncogenic growth factor, although the mechanism by which it stimulates the overproduction of myeloid cells characteristic of CML is unclear. It is probable that alterations in other proto-oncogenes dictate the eventual transformation of chronic phase CML to blast crisis.

The Ph chromosome also occurs in a minority of cases of acute leukaemia; the molecular changes are subtly different from those in CML.

**Fig. 1** Blood sample (right) from a patient with CML.

The greatly increased white cell component compared with the normal sample.

### CLINICAL FEATURES

Patients usually present in chronic phase. Typical symptoms are of anaemia, anorexia and weight loss. Splenomegaly is the most common physical finding and is often marked causing pain, bloating and satiety. The occasional patient presents with gout or hyperviscosity associated with a very high white cell count. Neutropenia and thrombocytopenia are not normally features of chronic phase and infection and haemorrhage are rare.

After a period of stability in chronic phase, patients develop blast crisis with symptoms typical of acute leukaemia. Between chronic phase (CP) and blast crisis is an intervening period of 'acceleration'. The accelerated phase is poorly defined but clinically is usually associated with an insidious deterioration in the patient's health and the need for more intense treatment to control splenic size and white cell count.

### DIAGNOSIS

The major laboratory abnormality in CP-CML is an elevated white cell count; this often exceeds  $100 \times 10^9/l$ . The blood film shows an increase in morphologically normal myeloid cells at all stages of differentiation but with greatest numbers of myelocytes and neutrophils. There is usually an absolute basophilia. Thrombocytosis and nucleated red cells may be present.

The bone marrow appearance is less informative than the blood film; pronounced hypercellularity and abnormal myelopoiesis is characteristic but not specific for CML. The key diagnostic abnormality is the presence of the Ph chromosome. In a few patients with apparent CML the Ph chromosome is absent. Such cases need careful review as they may represent an atypical myeloproliferative disorder or even chronic myelomonocytic leukaemia (a variant of myelodysplastic syndrome not to be confused with CML). The term chronic granulocytic leukaemia (CGL) is sometimes used to distinguish classical Ph positive CML from less typical forms of the disease. The accelerated phase is characterised by an increase in the number of immature cells in the peripheral blood and in blast crisis the blood appearance is dominated by the presence of myeloblasts (65% of cases) or lymphoblasts (35%). In the rare patients who present in blast crisis, the detection of the Ph chromosome may be the only clue as to the antecedent disease. Attempts at staging have been less successful than in some other haematological malignancies. The most widely used system devised by Sokal is based on patient age, spleen size, blood blast cell count and platelet count. The best predictor of survival is probably the response to initial therapy.

**Fig. 2** Blood film in CML showing myeloid cells of varying maturity

### MANAGEMENT

Recent advances have rendered the management of CML in chronic phase complex. Unfortunately, there has been less progress in the management of advanced disease.

#### Chronic phase

**Cytotoxic drugs.** The two conventional drugs are hydroxyurea and busulphan. These agents depress the white cell count, diminish splenic size and limit hypermetabolic symptoms. Hydroxyurea is the safer of the two drugs and most studies have suggested an improved survival compared with busulphan. Patients receiving cytotoxic drugs have survived an average of 3 to 7 years, although survivals exceeding 20 years are reported.

**Alpha interferon.** For patients not eligible for marrow transplantation, alpha interferon has now replaced oral cytotoxic drugs as first line treatment for CML. Its mode of action is poorly understood but clinical trials have shown a median survival advantage of 1 to 2 years for patients receiving regular subcutaneous injections of interferon compared with those receiving hydroxyurea or busulphan. Patients on interferon who achieve a good cytogenetic response (i.e. a fall in the percentage of Ph+ cells) or good control of the white cell count derive the greatest benefit. In good responders treatment should be continued indefinitely. Dosage regimens vary but dose escalation is often limited by side-effects including fever and other flu-like symptoms.

**Bone marrow transplantation (BMT).** Allogeneic BMT performed in chronic phase is the only proven curative treatment for CML. Patients have survived for more than 10 years after BMT with no detectable bcr-abl transcripts in blood or bone marrow studied with the polymerase chain reaction (PCR). The 5 year leukaemia free survival after HLA identical sibling BMT is between 50 and 60%. Results are best when BMT is performed within 1 year of diagnosis. Few clinicians perform allogeneic transplants in patients over 50 years old and only 30% of patients will have a matched sibling donor - thus only around 15% of CML patients are eligible for allogeneic BMT. In younger patients the use of an unrelated donor matched for HLA is possible but results are poorer than for sibling donor BMT with a higher incidence of graft versus host disease (GVHD). Autologous bone marrow or peripheral blood stem cell transplantation can induce Ph negative haematopoiesis and studies are underway to assess the impact on survival.

**Choice of treatment in chronic phase.** For patients less than 40 years old with an HLA identical sibling, allogeneic BMT remains the treatment of choice. For patients over 40 years or younger patients lacking a family donor, alpha interferon is first line treatment. In younger patients both lacking a family donor and failing on interferon, a search for an HLA matched unrelated donor should be considered. Other strategies in patients failing first line 'treatment' are hydroxyurea and autologous transplantation.

#### Advanced disease

In the accelerated phase and blast crisis options are limited. Patients may be helped by allogeneic BMT but results are much inferior to those achieved in CP. Blast crisis can be treated with the combination chemotherapy regimens used in acute leukaemia, and some patients (particularly those with lymphoblastic transformation) will initially respond and return to chronic phase. Unfortunately, such 'remissions' are usually short-lived.



### Chronic myeloid leukaemia

Sibling CML is a clonal myeloproliferative disorder arising from an acquired genetic change in a pluripotential stem cell.

The hallmark of CML cells is the Philadelphia chromosome (t(9,22)) and the resultant chimeric bcr-abl gene. There is gross overproduction of neutrophils and their precursors.

CML has an indolent chronic phase followed by a period of acceleration and a final, generally fatal, acute leukaemic phase.

### CHRONIC LEUKAEMIA

Chronic lymphatic (or lymphocytic) leukaemia (CLL) is a disease characterised by a clonal proliferation of B-lymphocytes. Although the malignant cells appear mature morphologically, they are actually arrested at an early stage of B-cell development. CLL is the most frequent form of leukaemia in the Western world and is a disease of the elderly; almost all patients are over 50 years old at diagnosis.

#### CLINICAL FEATURES

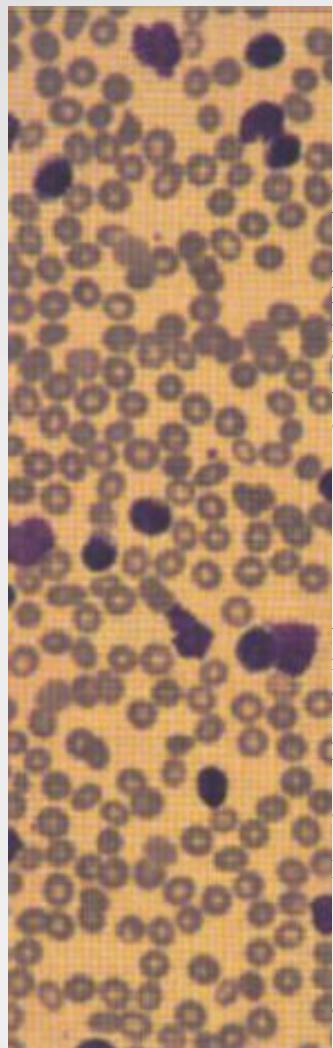
CLL is a highly variable disorder with many patients surviving long periods with minimal symptoms, whilst others have a rapid demise with bone marrow failure and bulky lymphadenopathy and hepatosplenomegaly. Fortunately, the former group are in the majority. Indeed, in up to three-quarters of cases the diagnosis is made by chance on a routine blood count. Elderly patients with CLL often die from other causes.

Where problems do arise, patients most commonly complain of symptoms of anaemia, lymphadenopathy, unusually persistent or severe infections, and weight loss. The most frequent findings on examination are lymphadenopathy (60%) and splenomegaly (25%). In more advanced cases other tissues such as skin, the gastrointestinal tract, the central nervous system, lungs, kidneys and bone may be infiltrated by leukaemic cells. Occasionally there is transformation into a poorly differentiated large cell lymphoma which carries a poor prognosis (Richter syndrome). The immunodeficiency in CLL is caused mainly by hypogammaglobulinaemia, which not only predisposes to infections but also accounts for an increased incidence of other malignancies.

**Fig. 1 a, b** CLL is a cause of acquired immuno-suppression. A: oral candidiasis, b: severe chickenpox

#### DIAGNOSIS

The diagnosis is suggested by a high lymphocyte count confirmed by the blood film appearance. Lymphocyte counts in CLL exceed  $5 \times 10^9/l$  and may reach levels of  $500 \times 10^9/l$  or more. The cells resemble normal mature lymphocytes but are often slightly larger with a tendency to burst during preparation of blood films, resulting in 'smear cells'. Unexplained lymphocytosis in an elderly person should always suggest the possibility of CLL. The diagnosis is made by proving that the lymphocytosis is a proliferation of clonal B-cells; this is most simply demonstrated by using in situ or flow cytometry techniques to show that the cells have characteristic B-lymphocyte



antigens and that a single immunoglobulin light chain (kappa or lambda) exists on the cell surface (i.e. it is a monoclonal population). The bone marrow aspirate shows increased numbers of small lymphocytes and a trephine biopsy is worthwhile as the pattern of lymphocyte infiltration gives prognostic information. If there is confusion with a low-grade non-Hodgkin's lymphoma, a lymph node biopsy can give useful histological information. The blood film appearance may suggest autoimmune haemolysis or autoimmune thrombocytopenia. Immunoglobulin levels should be checked to assess the degree of immunosuppression.

#### STAGING

Staging is important in CLL as it helps in making a rational decision as to whether to commence treatment, and it also gives useful prognostic information. The easiest method is the Binet adaptation of the previous Rai system; this is simple to apply and correlates closely with survival. Other variables can give additional prognostic information. A diffuse pattern of lymphocyte infiltration in the bone marrow, a very high number of lymphocytes in the blood, a rapid lymphocyte doubling time, a significant number of prolymphocytes in the blood, and an abnormal karyotype are all poor risk factors.

**Fig. 2** Blood film in CLL.

**Table 1 Binet staging system for CLL**

**Stage A** No anaemia or thrombocytopenia

Less than 3 lymphoid areas\* enlarged

**Stage B** No anaemia or thrombocytopenia

Three or more lymphoid areas enlarged

**Stage C** Anaemia (Hb less than  $100 \times 10^9/l$ ) and/

#### MANAGEMENT

##### When to start treatment

There has to be a reason to start treatment in CLL—many patients with early stage disease are completely well. Early treatment may slow progress but does not improve survival and can lead to significant side-effects including other neoplasms, and the emergence of resistant disease. Patients deserve a full explanation of the disorder. When the disease is early, they particularly need reassurance of its relatively benign nature.

##### Choice of treatment

In general, treatment should be commenced when the patient develops significant symptoms, when the disease is progressing rapidly or when it is already at an advanced clinical stage. The best single agent for initial treatment of CLL is chlorambucil. This is given orally and is probably better tolerated given intermittently than continuously. Prednisolone may be added but, in view of the multiple side-effects of steroids, it is better reserved for patients with pancytopenia, autoimmune haemolysis or thrombocytopenia. Combination chemotherapy (e.g. CHOP—cyclophosphamide, doxorubicin, vincristine, prednisolone) achieves a greater initial response rate than chlorambucil but this does not translate to an improved survival and it is best kept as second-line treatment.

A new class of drugs, the purine analogues, are already the treatment of choice where conventional treatment fails. The optimum agent appears to be fludarabine, which gives complete or partial remission in approximately half of previously treated patients.

Radiotherapy can be used as palliation, particularly where enlarged lymph nodes or spleen cause compressive problems. Splenectomy can be beneficial for painful splenomegaly or autoimmune cytopenia. In patients with hypogammaglobulinaemia and recurrent infections, regular intravenous immunoglobulin has been shown to be well tolerated and quality of life is often improved.

None of the above drug regimens or other treatment modalities will cure CLL; the emphasis is on control of symptoms and possible prolongation of life. In the rare younger patient with CLL a more aggressive approach to treatment may be justified to try and eradicate disease. Bone marrow transplantation from an allogeneic donor is potentially curative but experience is currently limited.

#### T-CLL

A small minority of cases of CLL (less T-rather than B-lymphocyte malignancies). The condition is usually associated with the appearance of large granular lymphocytes in the peripheral blood, neutropenia and splenomegaly. It is a relatively benign disorder although a few cases transform to a more malignant form.

#### Chronic lymphatic leukaemia

CLL is the commonest form of leukaemia in the Western world. It is a disease of the elderly.

In the usual form of the disorder, there is a clonal proliferation of B-lymphocytes (B-CLL)

Symptoms/signs include anaemia, recurrent infections, weight loss, lymphadenopathy and hepatosplenomegaly.

The clinical course is often indolent but it can be more aggressive in advanced stages.

Chemotherapy is often not immediately needed in early CLL.

Chlorambucil is the initial drug of choice in most cases. Purine analogues such as fludarabine are increasingly used in resistant and relapsing disease.



### HAIRY CELL LEUKAEMIA

Originally called 'leukaemic reticuloendotheliosis', this rare lymphoproliferative disorder is now more compellingly known as hairy cell leukaemia, a reference to the characteristic appearance of the malignant cell (Figs 1 & 2). The disease constitutes 2% of all leukaemias, occurs worldwide, and typically affects middle-aged men.

Hairy cell leukaemia (HCL) is usually a malignant proliferation of B-cells at a pre-plasma cell stage of differentiation. Most cases have clonally rearranged immunoglobulin genes and express relatively mature B-cell antigens. However, occasional cases express antigens typical of T-lymphocytes either alone or expressed with B-cell markers.

Fig. 1 'Hairy cells' in the blood

#### Clinical features

Patients often have non-specific symptoms including fatigue and weight loss. Infection, the main cause of morbidity and mortality, and bleeding are other possible presentations. The spleen is the probable site of origin of the malignant clone and splenomegaly is found in over 80% of cases. This may be massive and is usually not accompanied by lymphadenopathy. The liver is enlarged in 50% of patients.

#### Diagnosis

Most cases of HCL have a pancytopenia and there may be circulating hairy cells in the blood film. Neutropenia is often particularly marked accounting for the frequency of infection. The key cytochemical test is the demonstration of tartrate-resistant acid phosphatase (TRAP) activity in hairy cells. Morphology and cytochemistry are usually sufficient for diagnosis but testing with monoclonal antibodies may be useful - strong activity is seen with FMC7, CD25, CD11c and CD22. The bone marrow is normally difficult to aspirate because of increased fibrosis; the trephine will show a variable number of infiltrating hairy cells. Where splenectomy is performed, the sinuses and cords are seen to be infiltrated by a uniform population of lymphoid cells with blood-filled spaces lined by hairy cells (the pathognomonic 'pseudosinuses' of HCL).

CD25, CD11c and CD22. The bone marrow is normally difficult to aspirate because of increased fibrosis; the trephine will show a variable number of infiltrating hairy cells. Where splenectomy is performed, the sinuses and cords are seen to be infiltrated by a uniform population of lymphoid cells with blood-filled spaces lined by hairy cells (the pathognomonic 'pseudosinuses' of HCL).

Fig. 2 Hairy cells seen with electron microscope

#### Management

HCL is an unusual haematological malignancy in that there are a number of successful treatments available. The main challenge is in deciding which is most appropriate in an individual patient. A minority of patients (perhaps 10%) are asymptomatic and in the first instance may require no intervention. Treatment options are as follows.

#### Splenectomy

This is most helpful in patients with significant splenomegaly and limited bone marrow involvement. The procedure provides rapid palliation and improves survival. In around half of all cases there is a complete remission measured as normalisation of the blood count. Here additional therapy may be unnecessary.

#### Alpha interferon

Given subcutaneously daily or three times weekly, this agent reduces the hairy cell population in the bone marrow, diminishes blood cytopenia and improves quality of life and survival. Where tolerated, treatment should be

continued for at least a year. Major side-effects include initial worsening of neutropenia and systemic symptoms such as pyrexia, lethargy and depression. Following cessation, the disease normally slowly relapses but it will often respond to reintroduction of the drug.

**2-deoxycoformycin and 2-chlorodeoxyadenosine** These recently introduced agents have greater toxicity than interferon but are more effective in eradicating disease. Results so far suggest that limited courses of treatment give rapid clinical responses with a reduced relapse rate compared with interferon. One of these drugs is likely to become the treatment of choice for most patients.

Recent progress makes it difficult to give an accurate prognosis for HCL. Most patients can expect long-term survival.

### PROLYMPHOCYTIC LEUKAEMIA

Prolymphocytic leukaemia (PLL) may arise out of chronic lymphatic leukaemia but it more often presents *de novo* and is best regarded as a distinct disease. The malignant cell is usually of B-lineage and is more mature than the B-CLL cell. Thus, in addition to characteristic B-cell antigens, the cells show a high density of surface immunoglobulin and clonal rearrangements of both heavy and light chain immunoglobulin genes. Approximately 20% of cases are of T-cell lineage with T-cell receptor gene rearrangements and either a 'helper' or 'suppressor' cell phenotype.

#### Clinical features and diagnosis

PLL is very much a disease of the elderly with a maximum incidence in the eighth decade of life. The most common clinical presentation of B-PLL is massive splenomegaly. Lymphadenopathy is usually not conspicuous. In T-PLL, involvement of lymph nodes and other tissues including liver and skin is more common. The characteristic blood abnormality is a marked lymphocytosis (normally greater than  $100 \times 10^9/l$ ). Anaemia is normal but platelet numbers are often well preserved. Prolymphocytes are large cells recognised by their condensed nucleus with a single prominent nucleolus surrounded by abundant cytoplasm. B- and T-cell types are not distinguishable by routine microscopy but T-cells can be highlighted by acid phosphatase staining.

#### Management

PLL has a poorer prognosis than chronic lymphatic leukaemia - the median survival is 2 years with an even bleaker outlook in the T-cell variant. Most patients are elderly and the disease is frequently refractory to chemotherapy. Palliation of symptoms is the usual priority. Options include splenic irradiation, splenectomy and leucapheresis to control the high white cell count. Younger patients can respond to chemotherapy - a combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) is most used.

### ADULT T-CELL LEUKAEMIA

#### LYMPHOMA

Adult T-cell leukaemia lymphoma (ATLL) is a malignant disorder of relatively mature T-lymphocytes. It is rare but of great interest as it is conclusively caused by a virus. The majority of patients with ATLL have antibodies to HTLV-1 and definitive evidence for the aetiological role of this retrovirus has come from studies showing monoclonal integration of proviral DNA in the leukaemic cells. Unsurprisingly, the disease is mostly seen in areas endemic for HTLV-1, notably in parts of Japan and in the islands of the Caribbean. There is a long latent period from infection to overt disease with a cumulative risk of ATLL of around 40% in people infected before 20 years of age. Patients most commonly present in the fifth decade and, as its name suggests, ATLL may behave as leukaemia or a lymphoma. In the most acute form presentation is with a frank leukaemia. The malignant cells in the blood are pleiomorphic but often have very irregular polylobulated nuclei. Even within the leukaemic group there is great heterogeneity with chronic and smouldering forms. In 25% of cases the disease is better described as a lymphoma as there is no demonstrable blood involvement. Despite the variability of the pathology there are well-defined clinical and laboratory features which should prompt consideration of the diagnosis, particularly in a person from an HTLV-1 endemic area. In practice lymphoma type ATLL may be confused with other forms of T-non-Hodgkin's lymphoma. Leukaemic ATLL must be distinguished

from Sezary syndrome, a lymphoproliferative disorder with circulating T-cells and skin changes including erythroderma and exfoliative dermatitis.

#### Diagnosis

Diagnosis requires morphological examination and immunophenotyping of blood lymphocytes or a lymph node biopsy. HTLV-1 positivity is established by serological testing and by DNA analysis of affected tissue where available. Chromosome abnormalities are found in up to 90% of cases but are not specific for - ATLL.

#### Management

Treatment has been unsatisfactory and the median survival less than one year. The lymphoma type of ATLL has a slightly better outlook than the leukaemia type. Acute forms are frequently resistant to conventional high grade lymphoma chemotherapy protocols (e.g. CHOP). The combination of  $\alpha$  interferon and the anti-viral agent zidovudine is a novel treatment which may give responses where chemotherapy has failed. The chronic and smouldering - leukaemia forms can run a protracted course but eventually transform to an acute phase. Skin lesions may be helped by extracorporeal photochemotherapy.

#### Other leukaemias

Hairy cell leukaemia (HCL) is a malignant proliferation of B-cells with a characteristic hairy appearance. Pancytopenia and splenomegaly are common.

Possible treatments for symptomatic HCL include splenectomy, interferon and the new drugs 2-deoxycoformycin and 2-chlorodeoxyadenosine. The prognosis is usually good.

Prolymphocytic leukaemia is a B-cell (or less often a T-cell) malignancy typified by presentation in the elderly, a high white cell count, splenomegaly and a poor prognosis.

Adult T-cell leukaemia lymphoma is malignant disorder of T-lymphocytes caused at least in part by infection with the HTLV-1 virus. It may present as leukaemia or lymphoma.



Fig. 1 Purpuric rash in myelodysplastic syndrome

## THE MYELODYSPLASTIC SYNDROMES

The myelodysplastic syndromes (MDS) are a group of clonal disorders of the bone marrow. Their common feature is that the clone of cells derived from an abnormal stem cell maintains the capacity to differentiate, but this differentiation is ineffective and leads to a hypercellular bone marrow and peripheral blood cytopenia. Red cells, neutrophils and platelets may all be depleted. The ineffective haematopoiesis also causes characteristic morphological abnormalities in the marrow and blood which form the basis for diagnosis. During the course of MDS the abnormal clone is prone to lose its ability to differentiate and acute myeloid leukaemia (AML) intervenes. The disease was previously referred to as 'preleukaemia'. MDS is predominantly a disease of the elderly, although it may affect all ages. It may arise de novo or follow previous chemotherapy or radiotherapy for another malignancy. It seems to be increasing in incidence.

#### CLASSIFICATION

MDS is enormously heterogeneous. At the two extremes are a relatively benign anaemia and a disease resembling AML. The classification relies chiefly on the number of blast cells in the bone marrow and peripheral blood (Table 1). The divisions are inevitably rather arbitrary. Thus, the MDS subtype *refractory anaemia with excess blasts in transformation* (RAEB-t) is deemed to have evolved to AML when the marrow blast cell count reaches 30% of all nucleated cells. Division of the more benign subtypes *refractory anaemia* (RA) and *refractory anaemia with ring sideroblasts* (RARS) is made according to the number of ring sideroblasts in the marrow aspirate. RARS is a different disorder to the very rare congenital sideroblastic anaemia which usually produces a hypochromic microcytic anaemia. Occasionally, acquired sideroblastic anaemia is not primary (i.e. MDS) but secondary to alcohol misuse or drug treatment (e.g. antituberculous drugs). *Chronic myelomonocytic anaemia* (CMML) fits awkwardly into the classification as its definition is independent of the blast cell count and depends entirely on the presence of a peripheral blood monocytosis.

#### CLINICAL FEATURES

The diagnosis may be made on a routine blood count in an asymptomatic patient. Where symptoms do occur they range from a mild anaemia to the consequences of severe marrow failure with profound anaemia, leucopenia and thrombocytopenia. Abnormal haematopoiesis can cause functional abnormalities of cells and infection and haemorrhage may be more severe than would be predicted from the degree of cytopenia. Pronounced symptoms are predictably more common in the RAEB and RAEB-T subtypes. CMML, like the acute monocytic leukaemias, has specific features including splenomegaly (rare in other forms of MDS), skin infiltration and serous effusions.

#### DIAGNOSIS

##### Morphology

The diagnosis of MDS depends on careful morphological examination of the blood film and bone marrow aspirate and trephine specimens. Common abnormalities are as follows:

**Peripheral blood.** Red cells - anisopoikilocytosis, macrocytosis. Neutrophils - hypogranulation, pseudo-Pelger forms. Platelets giant forms.

**Bone marrow.** Erythroid cells - multinuclearity, nuclear budding, ring sideroblasts. Myeloid cells - hypogranularity, increased blast cells. Megakaryocytes- giant forms or micromegakaryocytes. Where there are changes in all three - lines the term 'trilineage dysplasia' is used. The bone marrow trephine biopsy usually confirms marrow hypercellularity, although fibrosis and even hypocellularity may occur.

#### Chromosomes

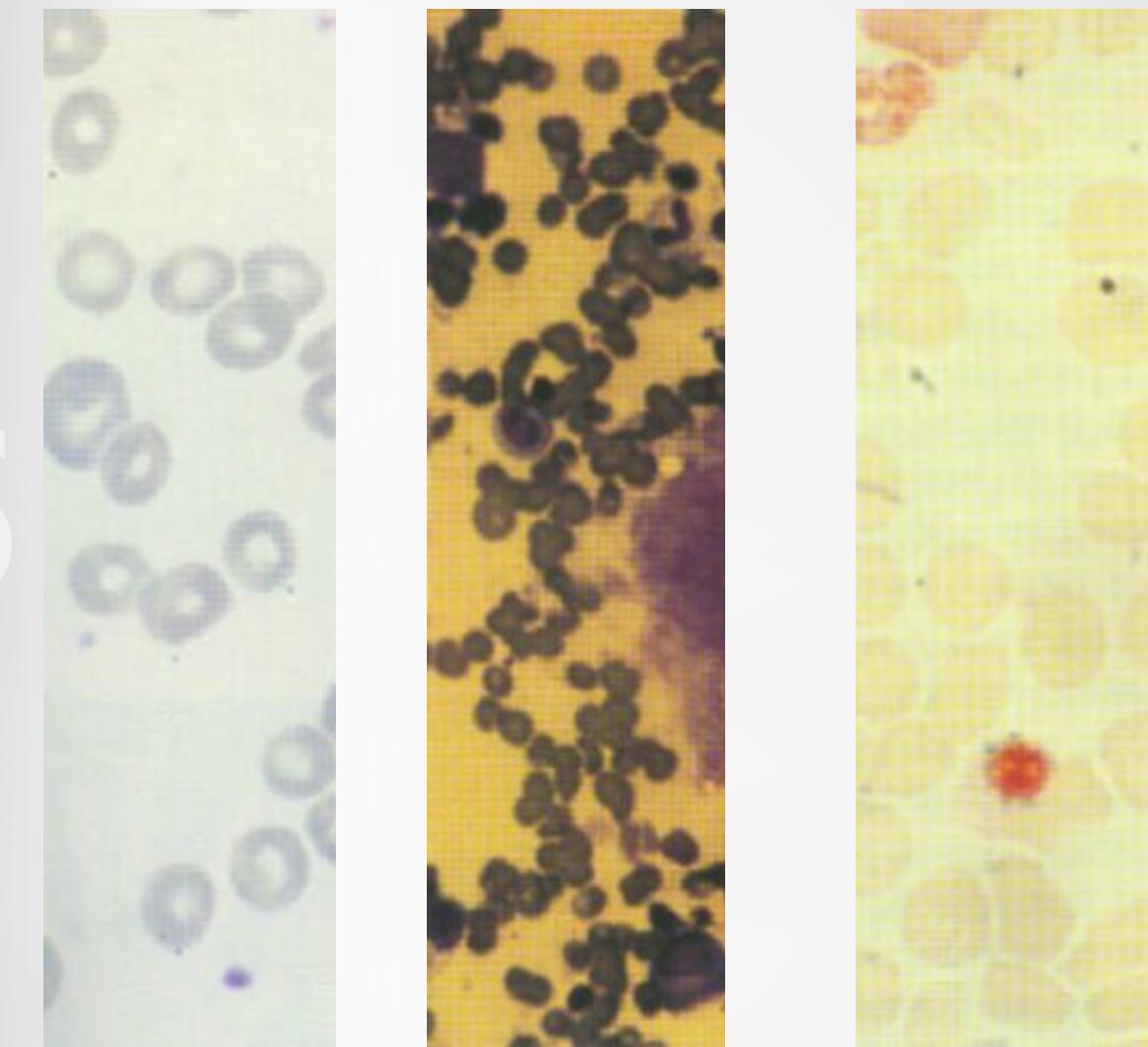
Up to 70% of cases of MDS show cytogenetic abnormalities. Common changes include monosomy 7 or 7q-, trisomy 8, monosomy 5 or 5q-, and loss of the Y chromosome. The 5q- abnormality is associated with a particular syndrome characterised by anaemia, macrocytosis, thrombocytosis and a relatively good prognosis. It is of interest that a number of genes important for normal haematopoiesis (e.g. GM-CSF, IL-3) are located on the long arm of chromosome 5. Monosomy 7 in children and young adults may represent a specific preleukaemic disorder with defective neutrophil function.

The most frequent molecular abnormality in MDS is a mutation of the Nras gene which is seen in up to 40% of cases.

Table 2 Relative incidence and prognosis

Type	Relative incidence (%)	Median survival (yrs)	Progress to AML (%)
RA	30	4	10
RARS	25	4	10
RAEB	20	1	40
RAEB-T	10	0.5	60
CMML	15	2	15

#### PROGNOSTIC FACTORS



The outcome is closely linked to the classification and the risk of leukaemic transformation (Table 2). Prognostic scoring systems have been devised which include severe blood cytopenia as an adverse factor. CMML is often an indolent disorder with mild anaemia but it may progress to acute monocytic leukaemia.

Fig. 2 a, b, c Myelodysplastic syndrome. (a): Pseudo-Pelger neutrophil with bilobed nucleus, (b): Dysplastic megakaryocyte in the bone marrow, (c): Iron stain of the bone marrow

## Haematopathology

#### TREATMENT

##### Supportive care

In patients with significant marrow failure, supportive care is crucial to ameliorate symptoms and prolong life. Regular blood transfusion is necessary to control symptoms of anaemia, and haemorrhage is managed with platelet transfusions. Infections require swift intervention with broad-spectrum antibiotics.

### Specific treatments

The only treatment currently offering the chance of prolonged remission and possibly cure is bone marrow transplantation from an allogeneic donor. Unfortunately, the majority of patients with MDS are elderly and this intensive procedure is not feasible.

### The elderly (over 60 years)

In most elderly patients the use of supportive care alone is reasonable. More specific treatments are designed to reduce cytopenia and slow progression to leukaemia, but real successes are rare. Corticosteroids may be worth a short trial and patients with the RARS subtype occasionally respond to pyridoxine. For more aggressive disease where a short survival is predicted (e.g. RAEB/RAEB-t) options include subcutaneous low dose cytosine arabinoside or single agent oral chemotherapy. Low dose cytosine may partly work by inducing differentiation of the malignant clone, but its major action is probably as a cytotoxic agent. Complete remissions are unusual but up to a third of patients will derive some benefit. Oral cytotoxic drugs including hydroxyurea, busulphan and etoposide have been used as single agents but with limited impact. Growth factors such as erythropoietin and G-CSF may reduce the degree of cytopenia and clinical complications and trials are currently underway.

### Children and younger adults

In children and younger adults with poor prognosis MDS, intensive combination chemotherapy is often justifiable. Initial response rates are high but remissions are usually short-lived. It may be that in MDS the residual normal stem cell pool is so much reduced that repopulation of the marrow with normal cells, and sustained remission, is impossible. The best chance of a prolonged remission follows an allogeneic bone marrow transplant. It has been suggested that in patients aged less than 40 years this procedure should be performed early before the development of a high leukaemic blast cell count or life threatening blood cytopenia. Where a suitable family donor is lacking, a search for an HLA matched unrelated donor may be undertaken.

### The myelodysplastic syndromes

MDS is a heterogeneous group of clonal disorders of the bone marrow; the abnormal clone differentiates ineffectively leading to a hypercellular marrow and blood cytopenia.

MDS may affect all ages but is predominantly a disease of the elderly.

Diagnosis depends on the presence of characteristic morphological changes in the blood and marrow.

Classification into subtypes relies on quantitation of blast cells in the blood and marrow.

Prognosis is highly variable dependent on the sub-type.

Elderly patients often receive only supportive care. In younger patients chemotherapy and allogeneic bone marrow transplantation may be justified.

### APLASTIC ANAEMIA

The term aplastic anaemia is a misnomer in that the disorder so described is characterised by a *pancytopenia* arising from failure of production of all the normal cells of peripheral blood. The underlying cause is a reduction in the number of pluripotential stem cells. This deficit may be exacerbated by an abnormality in the marrow microenvironment or an autoimmune reaction against the abnormal haematopoietic tissue.

Aplastic anaemia is uncommon (approximately 2-5 cases/ million/year worldwide), has a slight male predominance and affects all ages. The long-term survival of patient-, with severe disease was only 20% in the early 1970s but this has improved with the introduction of both immunosuppressive treatment and bone marrow transplantation.

It must be emphasised that aplastic anaemia is not a subtype of leukaemia. However, the disease's presenting clinical characteristics, the management problems of marrow failure (including fulminating septicaemia and haemorrhage) and the possible evolution to a clonal marrow disorder dictate its inclusion in this section of the book.

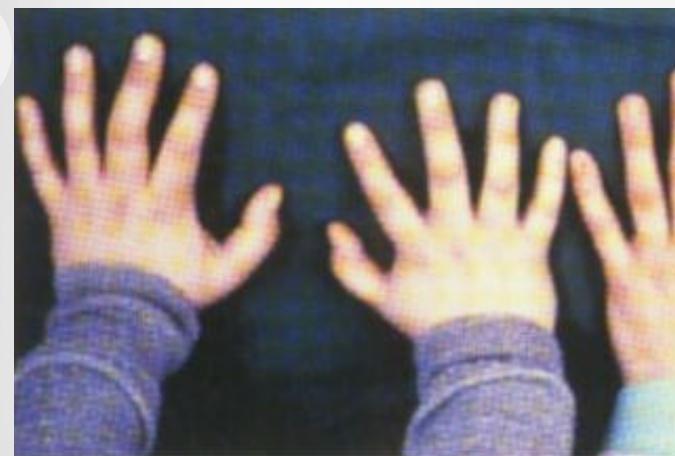


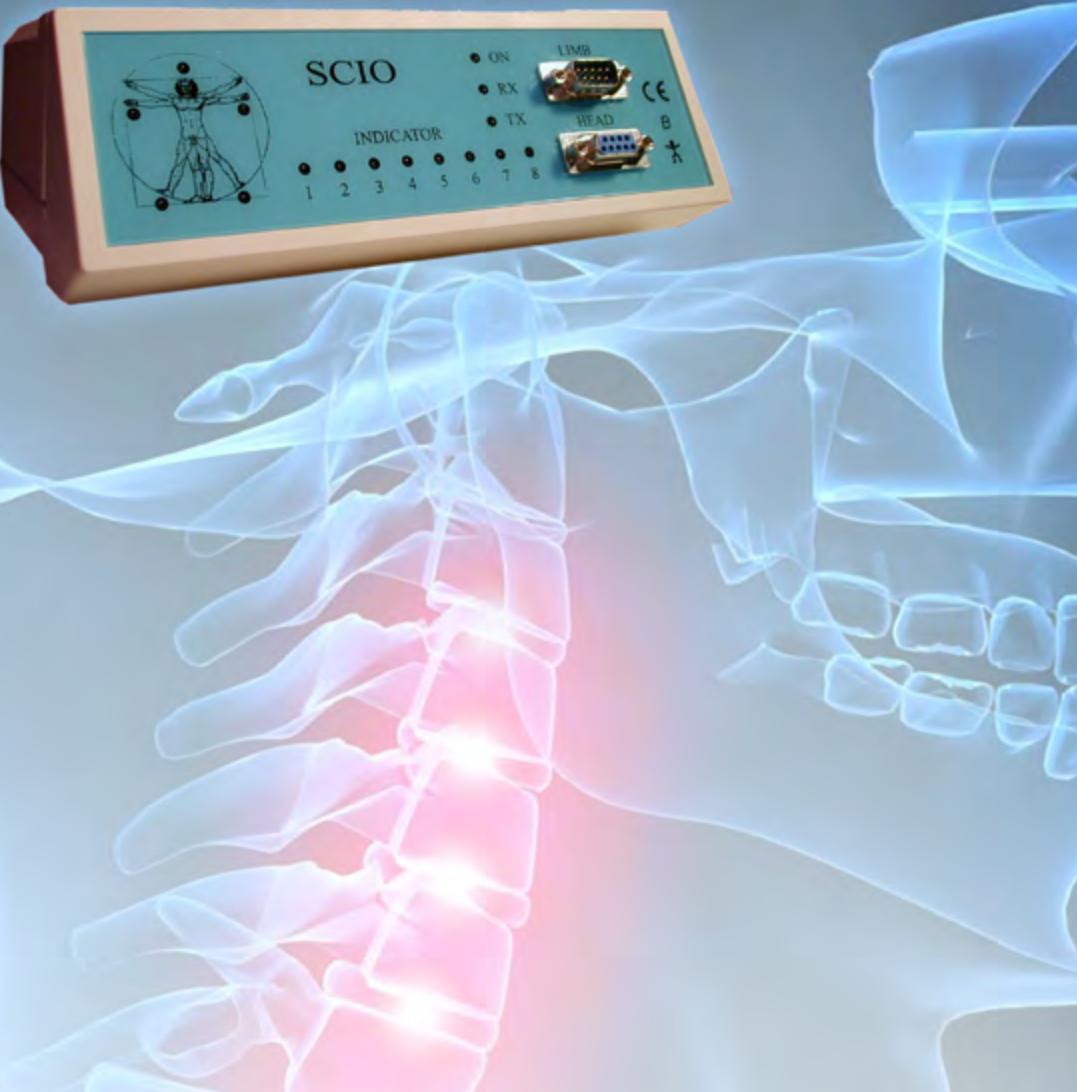
Fig. 1 Fanconi's anaemia, digital abnormalities

### CLASSIFICATION

Aplastic anaemia (AA) may be part of a congenital syndrome, be secondary to well-defined insults to the bone marrow, or arise apparently spontaneously with no identifiable cause. A simple classification is shown here. The most common congenital disorder is Fanconi's anaemia. Affected children suffer from defective DNA repair and the aplasia often coexists with skeletal deformities, skin pigmentation and renal abnormalities. Dyskeratosis congenital another form of constitutional aplasia, is distinguished by a later onset, nail dystrophy, leukoplakia of mucosal surfaces and a high incidence of epithelial tumours. Infections known to predispose to AA include viral hepatitis and parvovirus infection. Drugs and radiation can damage stem cells. Drugs may depress haematopoiesis idiosyncratically (e.g. chloram - phenicol) or predictably (e.g. chemotherapy). In roughly two-thirds of patients, no cause is apparent and AA is termed 'idiopathic'. Improved haematopoiesis following immunosuppression suggests that in at least some cases the abnormal stem cell compartment is further compromised by poorly defined immune phenomena.

Table 1 Classification of aplastic anaemia

1. Idiopathic AA



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identifying pathology

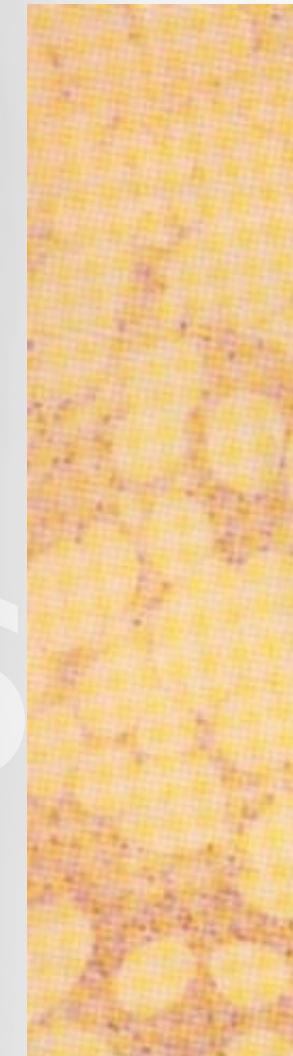


Fig. 2. Bone marrow trephine in several aplastic anaemia.

Congenital AA Fanconi's anaemia Dyskeratosis congenita

3, Secondary AA Drugs - idiosyncratic or dose-related Chemicals Ionising radiation Infection

### Table 2 Drugs associated with aplastic anaemia

Predictable	Cytotoxic agents
Idiosyncratic	Chloramphenicol

Sulphonamides

Phenylbutazone

Indomethacin

Gold salts

Penicillamine

Carbamazepine

Phenytoin

Acetazolamide

This is a selective list of more commonly implicated agents

### CLINICAL FEATURES

Patients with marrow failure predictably present with anaemia, unusually frequent or severe infections (caused by neutropenia) and a haemorrhagic tendency (caused by thrombocytopenia). The onset may be gradual or fulminant. Symptoms or signs of an underlying systemic disorder (e.g. Fanconi's) or possible trigger (e.g. hepatitis) may be present. An exhaustive history, including drug and occupational exposure, and a thorough examination are mandatory.

### DIAGNOSIS

There are really two questions. Is the pancytopenia due to aplastic anaemia? Is this idiopathic AA or aplasia secondary to an identifiable cause?

A reasonable sequence of investigations is as follows:

#### 1. Blood count and film

There is a pancytopenia and reticulocytopenia. Table 3 shows the differential - diagnosis of pancytopenia. In AA there are no abnormal circulating cells, simply a shortage of normal cells.

#### 2. Bone marrow aspirate and trephine

This is the key diagnostic test. The marrow aspirate can be highly suggestive of aplasia with grossly hypocellular particles but a trephine biopsy is necessary to confirm the diagnosis and quantify the degree of hypocellularity. Aplasia may be patchy and if the trephine is surprisingly cellular in the context of the blood count, then further samples should be obtained. In practice the only likely confusion is with hypocellular myelodysplastic syndrome or an atypical presentation of acute leukaemia, the latter particularly in childhood.

**3. Tests for an underlying cause** These include liver function tests (? hepatitis), viral titres (? recent infection), and a Ham test (? paroxysmal nocturnal haemoglobinuria). In childhood and adolescence special chronic studies are required to exclude Fanconi's anaemia.

#### 4. Other

Ferrokinetic studies will neatly demonstrate the marrow deficit but are rarely performed in practice.

#### MEASUREMENT OF SEVERITY

This is crucial as the severity defined from peripheral blood and bone marrow measurements predicts the response to treatment and survival. The median survival of untreated severe AA is 3-6 months with only 20% of patients surviving longer than one year.

#### MANAGEMENT

##### Removal of cause

Where an agent such as a drug or a chemical is implicated this should be removed.

##### Supportive care

Blood and platelet transfusion may be life-saving but should be used judiciously as patients with AA have intact cellular and humoral immunity and can become sensitised to histocompatibility antigens. Infection in neutropenic patients requires prompt expert management.

##### Restoring normal haematopoiesis

There are two major options, immunosuppression and bone marrow transplantation.

##### Immunosuppression

Although the precise mechanism of action is unknown, immunosuppressive agents provide worthwhile responses and prolonged survival in 50-70% of patients with AA. Responses are poorer in younger patients and in severe aplastic anaemia (SAA). Agents used include antilymphocyte or antithymocyte globulin (ALG/ATG), cyclosporin and Oxymethalone. The best regimen is probably a combination of ATG (given intravenously over 5-8 days with corticosteroids) and cyclosporin (given orally with monitoring of blood levels). Both drugs are potentially toxic - ATG can produce pyrexia, rashes and hypotension whilst cyclosporin may cause nephrotoxicity and hypertension. Responses to immunosuppressive treatment can take up to 4 months. Oxymethalone also has side-effects including virulisation, salt retention and liver damage. It is less effective than ATG and cyclosporin. As further discussed below there is concern that immunosuppression may often stimulate haematopoiesis but not cure the disease.

**Bone marrow transplantation (BMT)** The object of allogeneic BMT is to repopulate the patient's marrow with normal stem cells from a healthy compatible donor. Transplantation from an HLA identical sibling donor in younger patients (less than 45 years) produces long-term survival (possibly cure) in about 70% of cases. It is important to transplant early in the course of the disease as multiple transfusions lead to sensitisation and an increased chance of graft rejection.

##### Immunosuppression or BMT?

Younger patients (less than 20 years) with SAA and a matched sibling donor should be transplanted. In VSAA in this age group the lack of a family donor should prompt a search for a matched unrelated donor. In patients 20-45 years with SAA, sibling BMT and immunosuppression produce equivalent survivals over 2-5 years. However, a disturbingly high proportion of patients receiving immunosuppression alone, approximately 50% at 10 years, evolve to clonal marrow diseases such as paroxysmal nocturnal haemoglobinuria, myelodysplastic syndrome and acute myeloid leukaemia. Thus in this group matched sibling BMT gives a better long-term prognosis. In older patients with SAA, and patients with non-severe AA immunosuppression is generally the treatment of choice.

##### Growth factors

Growth factors cannot rectify the stem cell defect and are therefore not used alone in newly diagnosed AA. G-CSF or GM-CSF may, however, be useful in supportive care or in combination with ATG and cyclosporin.

#### Aplastic anaemia

AA is characterised by a pancytopenia arising from the failure of production of normal cells by the bone marrow. There is a reduction in the number of pluripotential stem cells; there may also be an abnormal marrow microenvironment and ill-defined autoimmunity. AA can be congenital, secondary to well-defined insults (e.g. drugs) or idiopathic. Prognosis relates to severity which is defined from blood and bone marrow indices. Evolution to a clonal marrow disorder such as leukaemia may occur. Good supportive care is vital. Major treatment modalities are immunosuppression and BMT - the choice of treatment is based on patient age, disease severity and availability of a marrow donor.

# CHEMOTHERAPY

## GENERAL PRINCIPLES

The life cycle of the normal cell is shown schematically in Figure 1. Antileukaemic (and antilymphoma) cytotoxic drugs can be broadly divided into those agents active during only one phase of the cell cycle ('phase-specific') and those acting at all stages ('phase non-specific'). In practice, most antileukaemic drugs act predominantly against proliferating cells and therefore affect only a fraction of the malignant cell population. Thus, if in advanced acute leukaemia the total number of malignant cells is  $10^{10}$ , a single course of chemotherapy could be expected to kill between 2 and 5 log of cells leaving between  $10^5$  and  $10^8$  residual leukaemic cells. It can be seen that the chance of eradication of the disease by chemotherapy is favoured by early treatment when the leukaemic mass is small and by repeated courses of cytotoxic drugs. It is also logical to combine different agents to maximise the antileukaemic activity and exploit different toxicities ('combination chemotherapy').

## MAJOR CLASSES OF CYTOTOXIC DRUGS

### Alkylating agents

Despite their variable structure, all alkylating agents appear to have a common mechanism with cross-linking of DNA the principal cytotoxic action. Alkylating agents commonly used in haematological practice include melphalan, chlorambucil, cyclophosphamide and busulphan. These agents are toxic to rapidly proliferating cells and the dose-limiting toxicity is myelosuppression with a nadir in the blood count 10-28 days after treatment. Other side-effects include infertility, haemorrhagic cystitis (cyclophosphamide) and an increased risk of secondary malignancy.

### Antimetabolites

These drugs are compounds which interfere with the utilisation of a natural metabolite by virtue of the similarity of their chemical structure. Most are analogues of nucleic acid precursors. Commonly used examples are the folic acid analogue methotrexate, the purine analogue 6-mercaptopurine, and the pyrimidine analogue cytosine arabinoside. The main toxic effect of the group is myelosuppression. The cytotoxicity of methotrexate can be partially reversed by

### Topoisomerase poisons

This broad class of drugs includes the anthracyclines (doxorubicin, daunorubicin, mitoxantrone, idarubicin) and the epipodophyllotoxins (etoposide). The anthracyclines are cell cycle non-specific drugs. The acute dose-limiting toxicity is bone marrow suppression but the cumulative dosage is limited by cardiotoxicity. Etoposide is a phase specific drug (active in G<sub>2</sub>) with myelosuppression the major toxicity.

### Spindle poisons

Key agents in this group are the vinca alkaloids, vincristine and vinblastine. They are cell-cycle phase-specific, exerting a cytotoxic effect by binding to cellular microtubular protein and inhibiting mitosis. Vincristine's major adverse effect is the causation of mixed motor sensory and autonomic neuropathies (patients usually initially complain of 'pins and needles' in the fingers or toes); vinblastine is less neurotoxic but causes more bone marrow suppression.

### Biological agents

The interferons are a family of proteins which have been shown to have anti-tumour activity in addition to an antiviral effect. They are divided on the basis of biochemical properties into three groups; alpha, beta and gamma. Alpha interferon is the most extensively studied in haematological malignancy and is well established in the

treatment of hairy cell leukaemia and chronic myeloid leukaemia. Side-effects include influenza like symptoms and a variable degree of myelosuppression. Interleukin 2 has been used experimentally in the treatment of advanced leukaemia; results of clinical trials are awaited.

## MAJOR SIDE-EFFECTS OF CYTOTOXIC DRUGS

Some toxic effects are common to many cytotoxic drugs and must be discussed with all patients receiving a relevant single agent or combination chemotherapy. Myelosuppression and alopecia are often unavoidable. However, nausea and vomiting can usually be minimised or even completely avoided by modern antiemetic protocols. The probability of infertility is influenced by the agents used, the total dosage, the duration of administration and the age and sex of the patient. Strategies to minimise infertility include prechemotherapy storage of germ cells (unfortunately, fertility is often abnormal at presentation) or choice of regimens which are relatively non-sterilising. Gonadal failure occurs more commonly in women and may be managed by hormone replacement therapy; androgens are used in men.

## NEWER AGENTS AND APPROACHES TO TREATMENT

There are two ways to improve the results of chemotherapy; firstly, by the modulation of the activity of currently available drugs, and secondly, by the introduction of new cytotoxic agents.

## BONE MARROW TRANSPLANTATION

The term 'bone marrow transplantation' (BMT) is loosely used to encompass a number of different procedures. It best fits allogeneic BMT where the marrow comes from another donor but is also used to describe autologous BMT where the patient's own marrow is used to reestablish haematopoiesis. The nomenclature has been further strained by the introduction of 'stem cell transplantation', where the haematopoietic stem cells are derived from blood rather than marrow. The subject is complex and can only be summarized here.

### ALLOGENEIC AND SYNGENEIC (TWIN) BMT

The allogeneic BMT procedure is outlined in Figure 2a. The patient's own haematopoietic stem cells, immune system and, hopefully, any residual turnout cells, are destroyed by high dose chemotherapy and (usually) radiotherapy ('conditioning treatment') prior to intravenous infusion of marrow harvested from the healthy donor. The ideal patient has a disease curable by allogeneic BMT but not by less toxic treatment and is young (less than 40 years). The ideal donor, excepting the presence of a twin, is a sibling genetically matched with the recipient for HLA-A, B and DR. The genes for HLA are found on chromosome 6 and thus inheritance follows the rules of simple mendelian inheritance; two siblings have a one-in-four chance of sharing the same HLA type. With relatively small family size in the Western world, only around 30% of patients will have an HLA identical sibling. In other patients it is possible to search large panels of unrelated HLA-typed volunteer donors for a phenotypic HLA match. The chance of successfully locating a matched unrelated donor largely depends on the frequency of the patient's HLA type in the population.

Following conditioning treatment there is a period of approximately 3 weeks before 'engraftment' during which the patient is severely pancytopenic and immunosuppressed and requires intensive supportive care with blood products and aggressive treatment of any infection. Major adverse events include graft rejection arising from a failure to immunosuppress the patient adequately, and graft-versus-host disease (GVHD). GVHD is a potentially life-threatening disorder predominantly affecting the skin, gastrointestinal tract and liver which may occur early after transplantation (acute GVHD) or after a few months (chronic GVHD). It is caused by donor immunocompetent cells attacking antigens in the recipient and can be abrogated by removal of T-lymphocytes from the donor marrow. Such 'lymphocyte depletion' also leads to an increased risk of relapse of any underlying malignancy, suggesting that some of the curative potential of the procedure is due to a 'graft-versus-tumour' effect. The profound immunosuppression of allogeneic BMT renders the patient vulnerable to pneumocystis pneumonia, cytomegalovirus and other opportunistic infections.

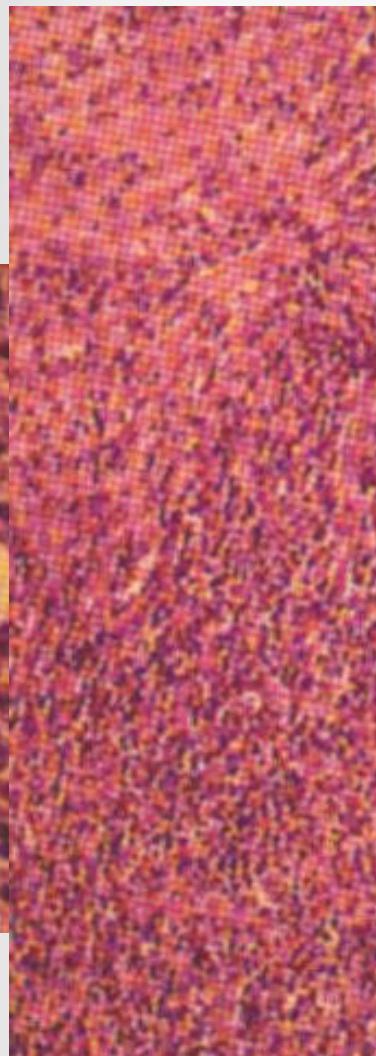
virus pneumonitis and other late viral infections. The indications for allogeneic BMT and results are discussed in the relevant disease sections.

#### AUTOLOGOUS BMT

The procedure is outlined in Figure 2b. High dose chemotherapy and radiotherapy is followed by reinfusion of previously stored patient marrow. Autologous BMT has less toxicity than allogeneic BMT and therefore can be performed in older patients. It also has the advantage, that the patient is the donor and therefore donor unavailability is not an issue. The main disadvantage of autologous BMT compared with allogeneic BMT is an - increased incidence of relapse of malignant disease. It is not clear whether this arises from resistance to the conditioning treatment or reinfusion of tumour cells in the graft. One approach is to 'purge' leukaemic cells from the marrow graft with cytotoxic drugs or monoclonal anti bodies but this is controversial. Indeed, the pro- the role of autologous BMT in both acute leukaemia and lymphoma remains unclear and further clinical trials are - needed.

#### Chemotherapy and bone marrow transplantation

There are several classes of cytotoxic drugs with different mechanisms of action. In leukaemia and lymphoma it is normal to combine agents in repeated courses to maximise anti-tumour activity and exploit different toxicities. Bone marrow transplantation (BMT) procedures may be undertaken using an HLA-matched family or unrelated donor (allogeneic BMT), an identical twin donor (syngeneic BMT), or the patient's own stored marrow (autologous BMT). Allogeneic BMT is a more effective anti-leukaemia treatment than autologous BMT but is associated with greater toxicity including possible graft rejection and GVHD.



## HODGKIN'S DISEASE

The lymphomas are malignant disorders of lymphoid tissue and are subdivided into two broad groups - Hodgkin's disease and non-Hodgkin's lymphoma.

Hodgkin's disease was first described by Thomas Hodgkin in 1832. In developed countries there is a bimodal age distribution with peak incidences in young adults (20-30 years) and the more elderly (over 50 years). The disease is almost twice as common in men.

#### AETIOLOGY

Hodgkin's disease is an unusual malignancy in that the malignant cells, termed Reed-Sternberg cells, and mononuclear Hodgkin's cells form only a minority of the tumour. The remainder is composed of very variable numbers of other cells including lymphocytes, granulocytes, fibroblasts and plasma cells. This inflammatory cell infiltrate presumably reflects an immune response by the host against the malignant cells. The nature of Reed-Sternberg (RS) and Hodgkin's cells has been extensively explored with conflicting results. It is likely that they are derived from lymphoid cells at an early stage of differentiation, either before or during the rearrangement of immunoglobulin and T-cell receptor genes.

Clustering of cases has been reported and Epstein-Barr virus DNA material is found in a minority of tumours. One hypothesis is that the bimodal distribution of Hodgkin's disease is due to infection in young adults with other environmental causes in older patients.

Fig. 1 Reed-Sternberg cells in a lymph node biopsy

#### CLASSIFICATION

Unlike the non-Hodgkin's lymphomas, the traditional classification of Hodgkin's disease is straightforward. The Rye classification divides it into four histological subtypes. In clinical practice the histological subtype is not crucial in the choice of treatment, although there are some correlations with presentation and prognosis.

#### CLINICAL PRESENTATION

##### Lymphadenopathy

Asymmetrical and painless lymphadenopathy, most often in- the cervical region, is the most common presentation. The nodes usually gradually enlarge but may fluctuate in size. Patterns of disease suggest contiguous spread via the lymphatic chain. Mediastinal involvement is a particular feature of the nodular sclerosing histological subtype. Splenomegaly and hepatomegaly occur but massive enlargement is rare.

**Fig. 2** Lymph node biopsy showing bands of collagenous tissue separating malignant cells.

#### Constitutional symptoms

Significant systemic upset affects a minority of patients (20-30%) at presentation. This includes fever, sweating (often at night), weight loss, pruritis and fatigue. A peculiar symptom is the development of pain at the site of disease after drinking alcohol.

#### Extranodal disease

Almost any organ can be infiltrated by Hodgkin's disease but at presentation extranodal spread is rarer than in nonHodgkin's lymphoma.

### DIAGNOSIS AND STAGING

#### Diagnosis

The key investigation is biopsy of a lymph node for histological examination. This is needed to distinguish Hodgkin's disease from other causes of lymphadenopathy.

#### Staging

Optimal treatment is determined by the stage of disease which is derived from the following investigations:

1. *Blood count and bone marrow investigation.* A mild normochromic or microcytic anaemia and blood eosinophilia may be present. Bone marrow aspiration and trephine biopsy to detect infiltration by disease is necessary in more advanced cases.
2. *CT scanning.* A whole body CT scan is now the central staging procedure. In difficult cases this may be supplemented by magnetic resonance imaging (MRI).
3. *Lymphangiography.* This is performed less often since the advent of CT scanning but can sometimes demonstrate disease in nodes of normal size on scanning.
4. *Laparotomy.* Laparotomy was previously routinely performed in patients with otherwise early stage disease to exclude abdominal involvement. Its use has dramatically declined with the introduction of better imaging techniques and other non-invasive methods for predicting response to treatment.

At the completion of staging investigations the patient is allotted a stage according to the Cotswold classification.

### MANAGEMENT

#### Early stage disease

Patients with stage I or II disease who lack adverse features such as systemic symptoms, an elevated erythrocyte sedimentation rate (ESR), multiple sites of involvement and/or bulky disease may be cured by *radiotherapy* alone. This is given over an extended field using a linear accelerator. Nodes above the diaphragm are treated using the 'mantle' field (like the mantle on a suit of armour) whilst the 'inverted Y' field includes all nodes below the diaphragm.

Where adverse features are present *chemotherapy*, either alone or combined with radiotherapy, is required. The classical regimen for treatment of Hodgkin's disease is the MOPP protocol (mustine, vincristine (Oncovin),

procarbazine, prednisolone) which is given at four-weekly intervals for a minimum of six cycles. Toxicity is significant and includes nausea, sterility and late secondary malignancy.

**Table 2 Factors predicting a poor prognosis**

- Advanced stage (most important)
- B symptoms
- Increased tumour bulk
- Increased sites of disease
- Advanced age
- Elevated erythrocyte sedimentation rate (ESR)
- Mixed cellularity Lymphocyte depleted histology

#### Advanced stage disease

All patients with stage III or IV disease require chemotherapy with possible addition of radiotherapy for bulky disease or palliation of symptoms. MOPP or a similar regimen may be used alone but the alternation of MOPP with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) is probably slightly superior. Higher dose chemotherapy may be given in an attempt to rescue patients relapsing after conventional treatment or as first-line treatment in younger patients selected for poor prognostic factors. Studies of autologous bone marrow transplantation and peripheral blood stem cell transplantation are underway.

### PROGNOSIS

Survival rates are closely linked to stage although within each stage other prognostic factors influence outcome (Table 2). Cure rates for early stage disease are around 85% whilst even more advanced disease is curable in up to 70% of patients with optimal management. As in other haematological malignancies, elderly patients tolerate chemotherapy less well and cure rates are more modest. In long-term survivors there is a risk of secondary malignancy, most commonly leukaemia and non-Hodgkin's lymphoma. The incidence of secondary cancer at 20 years is about 20% with the combination of chemotherapy and radiotherapy for advanced stage disease.

#### Hodgkin's disease

The term 'Hodgkin's disease' describes a group of lymphomas distinct from the 'non-Hodgkin's' lymphomas. The presumed malignant cells, Reed-Sternberg and mononuclear Hodgkin's cells, compose a minority of tumour cells.

Common clinical presentations are palpable lymphadenopathy and constitutional symptoms. Prognosis is largely determined by the stage of the disease. Early disease may be treated by radiotherapy alone. Advanced disease requires combination chemotherapy with the possible addition of radiotherapy.



## NON – HODGKIN'S LYMPHOMA

Malignant solid tumours of lymphoid tissue which are not Hodgkin's disease are termed non-Hodgkin's lymphomas (NHL). This group of lymphomas is even more heterogeneous than Hodgkin's disease and this complexity has led to a series of different classification systems, none entirely satisfactory. The disease is the most common haematological malignancy. In terms of years of life lost it is the fourth most important cancer in the Western world and it appears to be increasing in incidence. NHL may occur at any age but the median age of presentation is 50 years.

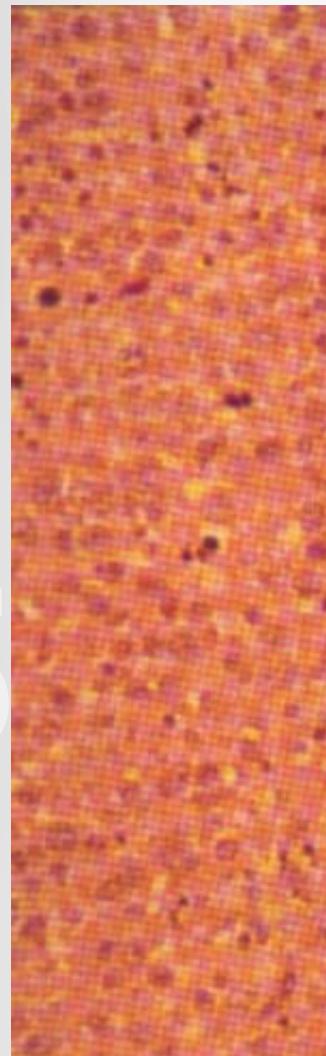
### AETIOLOGY

The cause of the majority of cases of NHL is obscure. However, specific chromosomal translocations are closely associated with particular histological types. Thus, the majority of Burkitt's lymphoma cases demonstrate the  $t(8, 14)$  abnormality in which the C-MYC oncogene on chromosome 8 is moved next to the immunoglobulin heavy chain region on chromosome 14. Over 90% of follicular low-grade lymphomas are characterised by  $t(14, 18)$  where the bcl-2 gene on chromosome 18 is moved to the immunoglobulin heavy chain region. This leads to excessive expression of bcl-2, an oncogene known to inhibit apoptosis (programmed cell death). It is likely that such chromosome rearrangements require further events - perhaps co-expression of a second proto-oncogene or antigenic stimulus - to produce the clonal malignant cell. An example of multiple events combining to produce a lymphoma occurs in patients with AIDS. The aggressive extranodal lymphomas seen are likely to result from a combination of immunosuppression (due to the HIV virus), deregulation of a proto-oncogene (c-MYC) and secondary viral infection (Epstein-Barr virus). Similar tumours may follow organ transplantation.

Fig. 1 Axillary lymphadenopathy in low-grade non-Hodgkin's lymphoma

Table 1 Histological classification (Working Formulation)

<b>Low grade</b>	A	Small lymphocytic with/without plasmacytoid differentiation
	B	Follicular small cleaved
	C	Follicular mixed small cleaved and large cell



<b>Intermediate grade</b>	D	Follicular large cell
	E	Diffuse small cleaved
	F	<b>Diffuse mixed small and large cell</b>
	G	Diffuse large cell
<b>High grade</b>	H	Large cell immunoblastic
	I	Lymphoblastic (convoluted/non-convoluted)
	J	Small non-cleaved cell (Burkitt/non-Burkitt)
<b>Other</b>		Miscellaneous types include composite malignancies and mycosis fungoides

Table 2 Classification based on approach to treatment

Type	Histological examples	
Indolent (low grade histology)	-	Small lymphocytic
	large cell	Follicular small cleaved
	Aggressive (intermediate or selected high grade histology)	Follicular mixed small cleaved and
	-	Diffuse small cleaved
	Aggressive with high risk of CNS and leukaemic relapse (selected high grade histology)	Diffuse mixed small and large cell
	-	Diffuse large cell
	-	Large cell immunoblastic
	-	Lymphoblastic
	-	Small non-cleaved cell

### CLASSIFICATION

Classification is complicated although some generalisations can be made. NHL is most crudely divided into 'high grade' and 'low grade' types. High grade tumours are composed of large poorly differentiated lymphoid cells and behave aggressively with rapid clinical onset and spread. Low grade tumours are composed of smaller better differentiated cells which are slower growing and accordingly have a more indolent clinical presentation.

The histological classification previously most widely used was the *Kiel Classification* in which NHL was divided into low and high grade types based on cell size with various subdivisions depending on the precise morphological appearance and the cell of origin (B or T-cell). The designation of the lymphoma cell (e.g. centroblast or centrocyte) presumed that it was fixed at an early stage of normal lymphocyte maturation. The most widely used classification system at present is the *Working Formulation* (Table 1). Here an additional intermediate category is inserted. Unfortunately even this classification does not accord entirely with current clinical practice. Table 2 is an adaptation of the Working Formulation for clinical use. It acknowledges that low grade tumours are indolent but usefully divides aggressive tumours on the basis of the likelihood of invasion of the central nervous system (CNS). This is more relevant to management than a histological label of 'high' or 'intermediate' grade.

NHL classification continues to evolve and the recent *'Revised European American Lymphoma' (REAL)* system is likely to become the accepted nomenclature.

### CLINICAL PRESENTATION

NHL is essentially a disease of lymph nodes but it has a more diverse presentation than Hodgkin's disease with more irregular spread and a higher incidence of extranodal involvement. It may be an indolent disorder, perhaps requiring no immediate treatment, or an aggressive rapidly fatal malignancy.

**Fig. 2** Section of cervical lymph node showing extensive infiltration with large poorly differentiated lymphoid cells

**Nodal involvement.** Painless lymphadenopathy, often in the cervical region, is the most common presentation of NHL.

**Extranodal involvement.** Symptoms and signs depend on the system involved. Intestinal lymphoma can present with vague abdominal pain, anaemia caused by bleeding or dysphagia. CNS disease frequently leads to headache and cranial nerve palsies and may cause spinal cord compression. Bone marrow involvement is more common in low grade lymphomas and can result in pancytopenia. Appearance of lymphoma cells in the blood is commonplace in low grade NHL but an ominous sign in high grade disease.

**Systemic symptoms.** Sweating and significant weight loss occurs in less than a quarter of patients and, where present, usually indicates advanced disease. Occasionally, patients present with metabolic complications such as hyperuricaemia, renal failure and hypercalcaemia.

#### DIAGNOSIS AND STAGING

**Diagnosis** depends on obtaining a tissue biopsy, usually a lymph node, for histological examination. Additional information is provided by use of monoclonal antibodies directed against specific lymphocyte associated antigens ('immunophenotyping') - these help identify the degree of maturation of the malignant cell and determine whether it is of B or T-cell origin. B-cell antigenic 'markers' include CD 19, 20 and 22 and T-cell markers CD 2, 3, 5 and 7. Gene rearrangement studies also aid identification. B-cell lymphomas have their immunoglobulin genes clonally rearranged whilst in T-cell **lymphomas** there is clonal rearrangement of the T-cell receptor genes. As previously noted, certain chromosomal abnormalities are characteristic of particular NHL subtypes.

The staging system is similar to that used in Hodgkin's disease. Patients are staged with CT scanning or MRI, and a bone marrow aspirate and trephine. However, in NHL the stage plays a more modest role in management than in Hodgkin's disease. The histological type of the tumour is more closely related to the likely clinical course and other factors impinge upon prognosis. This is particularly the case in high grade lymphoma where a number of prognostic factors can be considered together to predict 'high risk' disease with a poor response to conventional treatment. Indicators of a poor prognosis include advanced stage, extranodal disease, poor performance score and high lactate dehydrogenase (LDH) level.

#### MANAGEMENT AND PROGNOSIS

##### Indolent (low grade histology)

Patients may initially require no treatment - the situation is similar to early chronic lymphatic leukaemia. Localised disease may be treated with radiotherapy. Where systemic treatment is needed, the alkylating agent chlorambucil remains the agent of choice. Although initial response rates are high, the disease repeatedly relapses and median survival is between 6 and 10 years. More intensive combination chemotherapy, including autologous bone marrow or blood stem cell transplantation, is an option in younger cases. These regimens frequently prolong the time to relapse but cure and even a survival advantage compared with single agent treatment remain elusive. The failure to eradicate this apparently chemosensitive disease may be explained by the low mitotic rate of the turnout cells - cytotoxic treatment is relatively specific for rapidly proliferating cells. Newer agents such as alpha interferon and purine analogues (e.g. fludarabine) and forms of immunotherapy are currently being assessed.

##### Aggressive (high/intermediate grade histology)

Occasional patients with early stage disease lack poor risk factors and may be cured by radiotherapy alone. All others need chemotherapy and the standard regimen remains 'CHOP' (cyclophosphamide, doxorubicin, vincristine and prednisolone) given every 3 weeks for at least six courses. Around 60% of patients attain a remission on CHOP treatment but only 30-40% are cured. Merely increasing the number of cytotoxic drugs has not led to an improved chance of cure. An alternative approach is to identify high risk cases with poor prognostic factors who are unlikely to be cured with CHOP. Such cases may be treated with higher dose chemotherapy combined with autologous bone marrow or peripheral blood stem cell (PBSC) transplantation. This may also be the best treatment for relapse. Early results of PBSC autologous transplants with haematopoietic growth factor support suggest that this is a relatively

safe way of giving high doses of chemotherapy and the outcomes of larger studies are awaited. It should be noted that many patients with NHL are elderly and here even conventional chemotherapy doses are likely to be poorly tolerated.

##### Aggressive with high risk of CNS and leukaemic relapse (selected high grade histology)

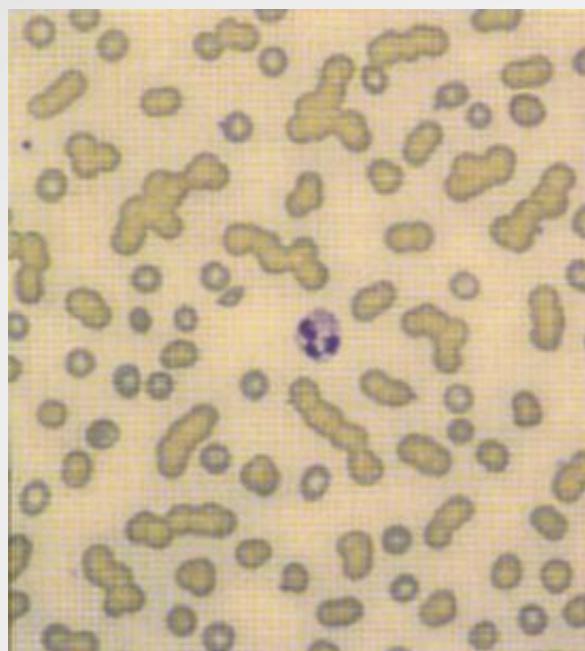
Treatment of these malignancies is particularly difficult. Most centres rely on drug regimens similar to those used in acute lymphoblastic leukaemia with additional CNS directed prophylactic therapy including intrathecal methotrexate and cranial irradiation.

##### Non-Hodgkin's lymphoma

The term NHL encompasses solid turnouts of lymphoid tissue which are not Hodgkin's disease.

Histological classification is complex. There is great clinical heterogeneity with aggressive types of disease. Indolent (low grade histology) NHL often initially responds well to chemotherapy (e.g. chlorambucil) but cure is elusive.

Aggressive (high/intermediate grade histology) NHL may be cured with conventional ('CHOP') chemotherapy; PBSC autologous transplants are increasingly used for 'high-risk' and relapsed disease.

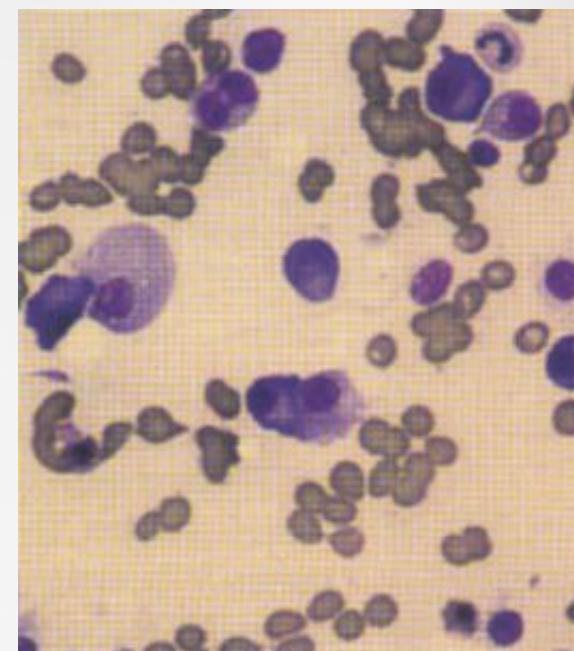


## MYELOMA

### INTRODUCTION

Multiple myeloma is a malignant disorder in which there is an uncontrolled proliferation of clonal plasma cells in the bone marrow. Secretion of a variety of proteins by the malignant cells leads to characteristic symptoms and signs. Myeloma constitutes 10-15% of all haematological malignancies and is essentially a disease of the elderly - only 2% of cases are diagnosed in patients less than 40 years old. For reasons that are unclear the disease is increasing in incidence.

**Fig. 1** Blood film in myeloma.



**Fig. 2** The bone marrow in myeloma

### BASIC BIOLOGY

Long viewed as a neoplasm of mature plasma cells, there is now evidence that the malignant cells are more immature, perhaps preceding B-cell lineage commitment or even at stem cell level. These cells secrete a monoclonal immunoglobulin or immunoglobulin fragments ('M-proteins') composed of a single heavy chain class and a single light chain class, kappa or lambda. Most myelomas produce IgG or IgA but light chains alone are produced in over 10% of cases. Free light chain appearing in the urine is termed Bence-Jones protein. Occasionally myeloma is non-secretory with no detectable M-protein. Although not routinely measured in clinical practice, the malignant cells also produce a variety of cytokines (e.g. interleukin6, tumour necrosis factor, osteoclast activating factor) which contribute to disease characteristics such as osteolysis, hypercalcaemia and renal failure.

### CLINICAL FEATURES

More than two-thirds of patients have bone pain at the time of presentation. Pain is most common in the back and chest and may be attributed to 'arthritis'. More advanced bone disease can lead to pathological fractures or vertebral

collapse with loss of height. Infiltration of the bone marrow by plasma cells may lead to symptoms of anaemia or bleeding due to thrombocytopenia. Infections are common due to immune paresis (low level of normal immunoglobulins) and other complications which may lead to symptoms include hypercalcaemia, amyloidosis and renal failure. The major cause of the nephropathy is deposition of obstructive tubular casts composed of immunoglobulin light chains - other possible factors include dehydration, infection and amyloid.

### DIAGNOSIS AND STAGING

It is worth restating that myeloma is an easy malignancy to miss as the early symptoms such as malaise and backache are common in the population. The combination of backache and a high erythrocyte sedimentation rate (ESR) should be taken seriously as it may indicate myeloma or another metastatic malignancy. Diagnostic criteria for myeloma are shown in Table 1. A pragmatic approach is to regard the minimum criteria as at least 10% immature plasma cells in the marrow or a plasma cytoma (local tumour composed of plasma cells), typical clinical features, and at least one of the following - an M-protein in the serum (usually greater than 3 g/l) or urine and lytic bone lesions on X-ray. Patients who have a paraprotein in the serum but do not meet the criteria for myeloma are said to have a '*monoclonal gammopathy of undetermined significance*' (MGUS). If followed up for 10 years, 10-20% of these patients than will develop myeloma. Monoclonal gammopathy can be associated with other diseases such as lymphoma, non-haematopoietic malignancies and connective tissue disorders. The prognosis of myeloma can be predicted from presenting clinical and laboratory features. The best known staging system (the 'Durie-Salmon') is based on the levels of haemoglobin, calcium, M-protein and Bence-Jones protein (BJP), and the extent of lytic disease



**Fig. 3** The fundus in hyperviscosity syndrome complicating Waldenström's macroglobulinaemia

### Table 2 Myeloma: poor prognostic factor

Low haemoglobin  
High calcium  
High M-protein or BJP level  
Multiple lytic lesions on X-ray

High creatinine (i.e. renal failure)  
High beta-2-microglobulin  
Low albumin  
Poor response to chemotherapy  
Included in the Durie-Salmon staging system

### MANAGEMENT AND OUTCOME

Myeloma may be diagnosed by chance on laboratory screening in patients with limited disease and no symptoms. In this group, about 20% of all patients, the disease may remain stable for several years and there is no advantage in early intervention. Where treatment is required this generally entails chemotherapy, management of specific complications, and palliation.

### Chemotherapy

There is virtually no prospect of cure of myeloma with current drugs. The standard first-line treatment is the alkylating agent melphalan, often combined with prednisolone. Both drugs are given orally in intermittent courses. Approximately 40% of patients will enter a remission, defined as a significant fall in M-protein and number of marrow plasma cells. The median duration of remission is around 2 years, the median survival 3 years, and less than 10% of patients live longer than 10 years. More aggressive combination chemotherapy regimens and other approaches such as high-dose steroid and alpha-interferon are being tried but remission rates and survival are not conspicuously better than with melphalan. Alpha-interferon may be more useful in prolonging remissions achieved with chemotherapy. In patients resistant to first-line treatment a combination of vincristine, doxorubicin (Adriamycin and dexamethasone (VAD) is the preferred option. Escalating the dose of melphalan to very high levels or other myeloablative therapy with autologous or allogeneic marrow transplantation may give at least short-term benefits to those younger patients able to tolerate the inevitable side-effects.

### Management of complications

The pain of bone disease may require local radiotherapy in addition to analgesia. In spinal compression, radiotherapy and high-dose steroids usually obviate the need for laminectomy. Biphosphates (e.g. pamidronate) inhibit osteoclast activity and are effective both in hypercalcaemia and in reducing bone pain. Renal failure often responds to rehydration and chemotherapy but haemodialysis may be required.

**Palliative treatment - a team approach** As there is currently little hope of cure, palliative care and emotional support are key issues. Cooperation is required between doctors, nurses and other healthcare workers in the hospital and community. Particular emphasis is placed on pain relief and the maintenance of independence.

### WALDENSTRÖM'S MACROGLOBULINAEMIA

This disease is a form of low-grade lymphoma. It is appropriately considered with myeloma as the malignant cells, which show features of lymphocytes and plasma cells, secrete an IgM paraprotein. The patient may complain only of fatigue, but high IgM levels can lead to the 'hyperviscosity syndrome' with confusion and neurological symptoms. In these cases retinal examination reveals engorged veins, haemorrhages, exudates and rarely papilloedema. Other possible physical signs include lymphadenopathy and hepatosplenomegaly. First-line therapy for symptomatic cases is chlorambucil or the purine analogue fludarabine which is also a useful new agent for resistant disease. Significant hyperviscosity requires plasmapharesis.

### Myeloma

Myeloma is a malignant proliferation of plasma cells.

Diagnostic features include an 'M-protein' in the serum and/or urine, osteolytic bone lesions and infiltration of the bone marrow by malignant plasma cells.

Bone pain is the most common presenting symptom.

Complications include renal failure, hypercalcaemia and amyloidosis.

Most chemotherapy regimens include melphalan. Cure is elusive. High-dose chemotherapy may prolong survival in younger patients.

Good palliative care, especially pain relief, is crucial.

Waldenström's macroglobulinaemia is a form of low-grade lymphoma with secretion of an IgM paraprotein and possible hyperviscosity.

## POLCYTHAEMIA

### INTRODUCTION

In simple terms, polycythaemia means an increase in red cell count, haemoglobin and packed cell volume (PCV) above the normally accepted levels. These measurements are routinely provided by automated cell counters. Polycythaemia due to an absolute increase in red cell mass may occur as a myeloproliferative disorder (polycythaemia rubra vera (PRV)) or secondary to hypoxia or an abnormal focus of erythropoietin secretion. In 'apparent polycythaemia' the raised haemoglobin and PCV are not accompanied by a significantly raised red cell mass; usually the plasma volume is relatively reduced.

### AN APPROACH TO THE PATIENT WITH POLCYTHAEMIA

This is summarised in Figure 2. The initial decision to investigate further is taken on the basis of a raised haemoglobin and PCV. If true polycythaemia is confirmed by measurement of red cell mass and plasma volume then the next step is to determine whether this is primary (i.e. PRV) or secondary. From the discussion of clinical syndromes which follows it will be seen that the full sequence of investigations is not required in all cases. For example, in a patient with known cardiac or respiratory disease causing chronic hypoxia, a degree of polycythaemia is predictable and does not require investigation.

### CLINICAL SYNDROMES

#### Polycythaemia rubra vera

PRV (or primary proliferative polycythaemia) is a myeloproliferative disorder; other diseases in this category are essential thrombocythaemia and idiopathic myelofibrosis. In PRV, a pluripotential stem cell is mutated. Although neutrophils and platelets may also be produced in excess, polycythaemia is dominant.

**Clinical features.** The raised red cell mass and total blood volume with associated hyperviscosity causes the symptoms and signs of the disease. Common complaints include headaches, dizziness, lethargy, sweating and pruritis (the latter particularly after a hot bath). Most importantly, there is an increased risk of arterial and venous thrombosis, particularly strokes. Paradoxically, a combination of hyperviscosity and platelet dysfunction can cause a bleeding tendency in some patients. The increased cell turnover may lead to gout. Patients are characteristically plethoric and may have rosacea. Splenomegaly is present in 75% of cases.

**Diagnosis.** The diagnostic challenge is to differentiate PRV from a secondary polycythaemia. Splenomegaly is highly suggestive of PRV. In PRV the white cell and platelet counts are often also elevated and the increased erythropoiesis can lead to iron deficiency and hypochromic microcytic red cells. Erythropoietin estimation by radioimmunoassay is normal or low. The bone marrow aspirate and trephine in PRV show hypercellularity but there are no pathognomonic features; in about 15% of cases there is an abnormal chromosomal karyotype (e.g. 20q-). Diagnosis of less florid cases of PRV relies on the systematic exclusion of other causes of polycythaemia such as hypoxia (check chest X-ray and blood gases) and renal disease (screen urine and renal ultrasound or intravenous pyelogram).

**Management.** The dual purpose of treatment is to relieve symptoms and to reduce the risk of complications such as thrombotic disease and bleeding. The aim is to reduce the PCV below 0.45. This is most easily attained by venesectiions (up to 450 ml of blood removed) which may initially be required twice weekly. Many patients need no other treatment. In more severe disease the requirement for venesection can become intolerable and cytotoxic drugs are used to suppress erythropoiesis. Hydroxyurea is the usual choice. Busulphan and radioactive phosphorus are effective given intermittently but both are best avoided in younger patients as there is a significant risk of secondary malignancy. Drug treatment is particularly important when there is a need to control coexistent thrombocytosis.

PRV is a relatively benign haematological disorder and if well-controlled is compatible with a median survival of greater than 10 years. However, it is a clonal disease and a few patients eventually transform to myelofibrosis (15%) or even acute leukaemia (5%). The risk of the latter is increased by treatment with alkylating agents (e.g. busulphan).

#### Secondary polycythaemia

This is due to either a physiological response to hypoxia or an inappropriate secretion of erythropoietin. Treatment is essentially that of the underlying cause, although cases with very high PCVs may benefit from venesection.

#### Idiopathic erythrocytosis

These are a heterogeneous group of patients who have an absolute polycythaemia without features of either PRV or secondary polycythaemia. Occasional cases are familial.

#### Apparent polycythaemia

Apparent polycythaemia, where the red cell mass is within normal limits, is more common than PRV. This condition has accumulated several names including spurious, stress or relative polycythaemia, pseudopolycythaemia and Gaisbock's syndrome. Plasma volume is usually in the low normal range with only 20% of cases being below normal. Thus the usual cause of apparent polycythaemia is an increase in red cell mass and a decrease in plasma volume within the normally accepted limits. Patients are most frequently male and middle aged. Other common characteristics are excess weight, hypertension, diuretic use and significant consumption of alcohol and tobacco. The adoption of a healthier lifestyle often leads to resolution of polycythaemia. Most clinicians start venesection at PCVs exceeding 0.54 with a view to maintaining the level below 0.45 and reducing the risk of vascular occlusion.

#### Polycythaemia

Polycythaemia means an increase in haemoglobin and PCV above normally accepted limits.

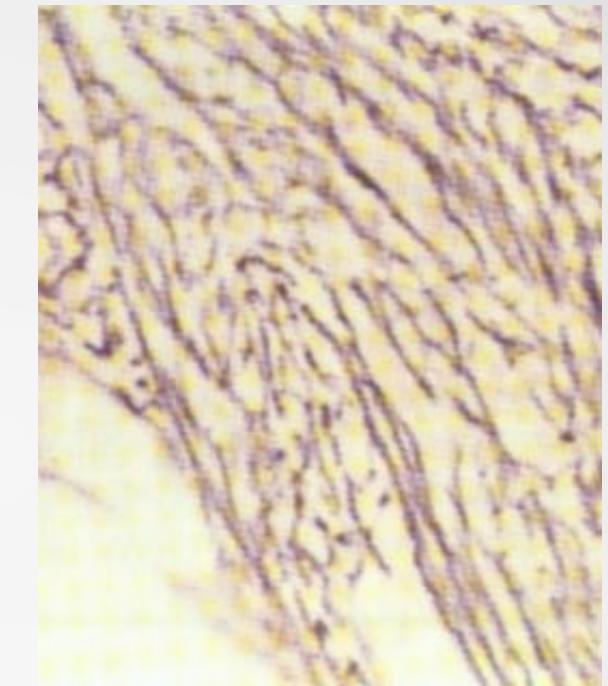
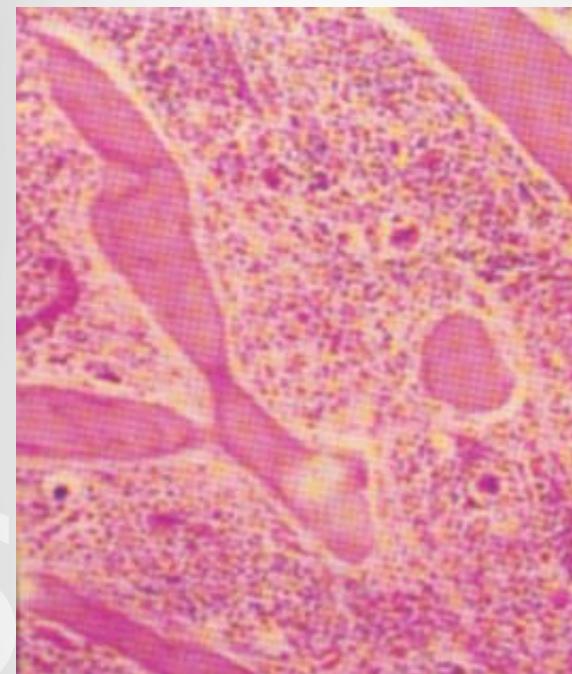
Polycythaemia can be absolute (with an increased red cell mass) or apparent (with a normal red cell mass). The absolute form can be primary or secondary.

Primary polycythaemia is myeloproliferative disorder (polycythaemia rubra vera). Secondary polycythaemia arises from a physiological response to hypoxia or inappropriate secretion of erythropoietin.

Management of PRV is by venesection alone or with cytotoxic drugs.

Treatment of secondary polycythaemia is essentially that of the underlying cause.

Apparent polycythaemia may respond to adoption of a healthier lifestyle.



### ESSENTIAL THROMBOCYTHAEMIA AND MYELOFIBROSIS

Essential thrombocythaemia (ET) is a myeloproliferative disorder characterized by a persistent increase in platelet count. There is a probable defect in the pluripotential stem cell with a resultant excess platelet production of up to 15 times normal. ET may be associated with either thrombotic or haemorrhagic complications, the latter caused by abnormal platelet function. As there is no specific diagnostic test, diagnosis relies upon exclusion of other causes of a high platelet count. The average age of presentation of ET is around 60 years with an equal incidence in both sexes.

**Fig 1** Bone marrow trephine biopsy in myelofibrosis (a) marked fibrosis and osteosclerosis, (b) increased reticulin fibres

#### CLINICAL FEATURES

ET may be asymptomatic and discovered accidentally on routine blood testing. Symptoms commonly stem from disturbances of the microcirculation. Patients may complain of burning sensations in the soles and palms, cold peripheries and varied neurological symptoms including headache and dizziness. Arteriolar occlusion can cause ischaemia, gangrene or acrocytosis. Thrombosis of large arteries is of even greater concern. Haemorrhagic problems include ecchymoses, epistaxis, menorrhagia and bleeding into the mouth and gut. Splenomegaly is unusual at least in part because of splenic infarction, which can be painful.

#### DIAGNOSIS

Platelet counts can be as high as  $1500 \times 10^9/l$  and usually exceed  $600 \times 10^9/l$  (the normal range is  $150-400 \times 10^9/l$ ). In practice, there is no single test to identify ET - diagnosis is a process of exclusion. As thrombocytosis may accompany a wide range of disorders including infections, inflammatory conditions and malignancy, a thorough history and examination is mandatory. The lack of a measurable 'acute phase response' (i.e. normal erythrocyte sedimentation rate, plasma viscosity and fibrinogen) increases the likelihood of ET as opposed to a 'reactive' thrombocytosis. High platelet counts are also seen in other myeloproliferative disorders, and bone marrow examination is worthwhile to exclude chronic myeloid leukaemia (absence of Philadelphia chromosome). Patients

with polycythaemia rubra may have thrombocytosis, while patients with ET can have an increased red cell mass. In clinical practice both such patients are better diagnosed as having myeloproliferative disorders rather than forced into either category. Only about 5% of all raised platelet counts are due to ET, but persistence of the count above 1000, particularly with coexistence of thrombosis or haemorrhage, makes it the likely diagnosis. Abnormal platelet function tests with reduced aggregation to adrenaline suggest ET rather than a reactive thrombocytosis.

#### MANAGEMENT

The treatment of ET is not straightforward. The decision whether to treat at all must follow consideration of the patient's age, the degree of thrombocytosis and the presence or perceived risk of significant thrombotic or haemorrhagic events. Any clinical benefit must be weighed against potential toxicity of cytotoxic drugs. In a patient with a very high platelet count (greater than 1000), characteristic symptoms, or a history of thrombotic/haemorrhagic disease, chemotherapy is indicated to reduce the platelet count. Conventional drugs include busulphan and hydroxyurea while newer agents such as interferon and anagrelide are under investigation. The objective of treatment is to reduce complications by maintaining the platelet count in the normal range. Where thrombotic problems persist the addition of low-dose aspirin may be helpful. There is a case for observation alone in asymptomatic patients with lower counts - particularly in younger patients who seem to have less complications and in whom the risks of long-term cytotoxic drug therapy are considerable. Occasionally, cases of ET transform to acute leukaemia. This is more common where alkylating agents have been used.

#### MYELOFIBROSIS

Idiopathic myelofibrosis is a myeloproliferative disorder characterised by bone marrow fibrosis and splenomegaly. Patients are usually older than 50 years and there is an equal sex incidence. Like ET, myelofibrosis is a neoplastic clonal disorder originating in a single pluripotential stem cell. Abnormal megakaryocytes are produced in increased numbers and it is these cells which release the cytokines, platelet-derived growth factor (PDGF) and platelet factor 4 which stimulate fibroblast proliferation and build-up of collagen in the bone marrow. The scarred marrow is unable to function normally and haematopoietic stem cells move to the spleen and liver (extramedullary haematopoiesis).

#### CLINICAL FEATURES

The disease is often insidious in onset with fatigue and weight loss. Splenomegaly is present in all cases and massive in 10%. Splenic pain is common and a bulky spleen may lead to portal hypertension, bleeding varices and ascites. Hepatomegaly is seen in two thirds of cases.

#### DIAGNOSIS

Sclerosis of bones is common and when X-rays show dense bones in a patient with splenomegaly, myelofibrosis is the likely diagnosis. Anaemia is almost universal and the blood film shows tear-drop poikilocytes and a 'leucoerythroblastic' picture with nucleated red cells and immature myeloid cells. In the early stages, thrombocytosis and neutrophilia may occur but in more advanced disease low counts are the rule. Bone marrow aspiration characteristically results in a dry tap (i.e. only peripheral blood aspirated), and a marrow trephine showing dense reticulin fibres on silver staining, fibrosis and osteosclerosis is needed for diagnosis. There is usually megakaryocytic hyperplasia. The major differential diagnosis is from other myeloproliferative disorders and myelodysplastic syndromes which may be associated with marrow fibrosis. Systemic causes of marrow fibrosis such as marrow infiltration by carcinoma or lymphoma and disseminated tuberculosis should also be considered. Acute megakaryocytic leukaemia (AML M7) is sometimes termed 'acute myelofibrosis' but it has a presentation more in to acute myeloid leukaemia.

#### MANAGEMENT

Asymptomatic patients may require no treatment. For anaemia a trial of a corticosteroid or androgen is worthwhile but patients usually become dependent on regular transfusion. Cautious use of oral chemotherapeutic agents such as busulphan and hydroxyurea can improve quality of life by reducing systemic upset and shrinking the spleen. Alpha interferon has been found to be helpful in a few cases.

Splenic irradiation can be used to alleviate splenic pain. Splenectomy must not be undertaken lightly as it is associated with considerable mortality (around 20%). However, it should be considered where there is painful splenomegaly, unacceptable transfusion requirements, life threatening thrombocytopenia or complications of portal hypertension.

Bone marrow transplantation is the only potentially curative procedure but is unfortunately limited to the rare younger patient with a matched donor.

#### Essential thrombocythaemia and myelofibrosis

ET is a myeloproliferative disorder characterised by a persistent increase in platelet count.

ET patients may be asymptomatic or have either thrombotic or haemorrhagic complications.

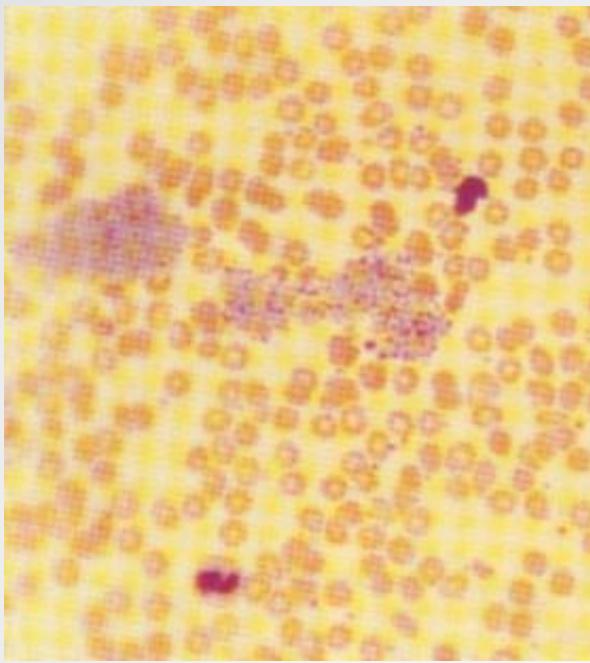
The object of treatment with cytotoxic agents (e.g. hydroxyurea) in ET is to reduce complications by maintaining the platelet count in the normal range.

Myelofibrosis is a myeloproliferative disorder characterised by bone marrow fibrosis and splenomegaly.

Common symptoms in myelofibrosis are fatigue, weight loss and splenic pain.

Treatment of myelofibrosis is problematic. Regular transfusion is often needed for anaemia.

Cautious chemotherapy, splenic irradiation and splenectomy can relieve symptoms in some patients.



## THROMBOCYTOPENIA

Thrombocytopenia can be simply defined as a blood platelet count of below  $150 \times 10^9/l$ . With the routine measurement of platelet number by automated cell counters it is a relatively common laboratory finding. Before initiating further investigations it is important to confirm that a low platelet count is genuine by careful inspection of the blood sample and film. Either a small clot in the sample or platelet clumping (Fig. 1) can cause artefactual thrombocytopenia and lead to unnecessary intervention.

### CAUSES

Major causes of thrombocytopenia are listed in Table 1. Some of the diseases (e.g. leukaemia) and syndromes (e.g. disseminated intravascular coagulation (DIC)) are discussed elsewhere. In general terms there are four possible processes leading to thrombocytopenia.

**Failure of marrow production.** The bone marrow failure of haematological disease (e.g. aplastic anaemia, leukaemia) usually causes pancytopenia. However, thrombocytopenia may be the only sign of intrinsic marrow disease or marrow suppression associated with infection or chemotherapy.

**Fig. 1** Blood film showing clumping of platelets.

**Shortened life span.** Platelets can be destroyed in the circulation. The most common mechanism is an immunological reaction in clinical syndromes such as idiopathic thrombocytopenic purpura (ITP) and various connective tissue disorders. Infections and drugs may also cause immune platelet destruction. In DIC, platelets are destroyed as part of an abnormal activation of the coagulation system.

**Sequestration.** Splenomegaly can cause low platelet counts because of pooling in the enlarged organ. The spleen is not necessarily massively enlarged.

**Dilution.** Normal platelets are diluted by massive blood transfusion. This happens because platelets are unstable in the conditions of normal blood storage.

### CLINICAL PRESENTATION

Patients with thrombocytopenia are particularly prone to bleeding from mucous membranes. It should be emphasized that spontaneous bleeding is usually only seen with platelet counts of less than  $10-20 \times 10^9/l$ , although patients with associated platelet dysfunction may bleed at higher counts. Conjunctival haemorrhage and nose and gum bleeding are all relatively common, with haematuria, melaena and severe menorrhagia less frequent complications. Intracranial bleeding is of serious import but, thankfully, is rare. Possible examination findings include purpura and more extensive petechial haemorrhages involving the skin and mucous membranes. The retina should be routinely inspected for haemorrhages.

### CLINICAL SYNDROMES

#### IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

ITP is a disease characterized by immunological destruction of platelets. It is conventional to divide the disorder into two discrete entities: acute ITP and chronic ITP. This division is convenient for discussion of pathogenesis and apt for most patients, but in 'real life' there is overlap between the two syndromes.

#### Acute ITP

The acute form of the disease is usually seen in childhood. It typically has an abrupt onset a week or so following a trivial viral illness. It is likely that in postviral cases IgG antibody attaches to viral antigen absorbed onto the platelet surface. The resultant sudden fall in platelet count (often to below  $20 \times 10^9/l$ ) can lead to all the symptoms and signs quoted above. Despite this, serious complications such as intracranial bleeding are very rare and the disease is self-limiting in around 90% of cases. Often only observation is required, but where the bleeding tendency is unusually severe, oral corticosteroids or intravenous immunoglobulin can be given as in chronic ITP. A few children go on to develop chronic thrombocytopenia, but even here the disease is relatively benign and many eventually spontaneously remit.

#### Chronic ITP

Autoantibodies against platelet membrane antigens are detectable in about 80% of patients with chronic ITP. Most are targeted against epitopes on glycoprotein IIb/IIIa which is the most frequent and most immunogenic platelet surface glycoprotein. Platelets sensitised with autoantibody (usually IgG) are destroyed by macrophages in the spleen and liver.

Chronic ITP is most common in young women. Patients may be asymptomatic or have insidious onset of bleeding problems. Serious spontaneous bleeding is generally limited to where the platelet count is below  $10 \times 10^9/l$  and even then it is unusual. A palpable spleen suggests a diagnosis other than ITP.

The blood film confirms thrombocytopenia; often the platelets are increased in size. A bone marrow aspirate and trephine biopsy show normal or increased numbers of megakaryocytes. There is no routine specific test for ITP although some laboratories are able to detect platelet antibodies using recently developed methods. Other investigations are designed to exclude a co-existent systemic disorder; an autoantibody screen (connective tissue disorder), and anticardiolipin antibodies and a lupus anticoagulant screen (antiphospholipid antibody syndrome) should be checked. HIV infection can cause immune thrombocytopenia and must be considered where patients are at risk. In younger patients congenital thrombocytopenias may be confused with ITP. A thorough drug history is essential.

Patients with asymptomatic mild thrombocytopenia can be merely observed. It is difficult to state a platelet count below which treatment is mandatory  $30 \times 10^9/l$  has been suggested but many patients are symptom free even at this level. The normal first line treatment is prednisolone (1 mg/kg body weight). About two-thirds of patients have a significant increase in platelet count within weeks but subsequent dose reduction often leads to relapse. Where there is no response to steroids, an intravenous infusion of immunoglobulin can be efficacious. Platelet transfusions are seldom indicated as the platelets are rapidly destroyed but they may be considered in severe haemorrhage. If the platelet count cannot be maintained at a satisfactory level on non-toxic doses of corticosteroid then splenectomy is usually performed. It may be delayed a few months to allow for the small possibility of a spontaneous remission. About two-thirds of patients have a good response. The management of severe/symptomatic thrombocytopenia postsplenectomy is difficult. An accessory spleen should always be excluded. Where treatment is considered necessary a relatively non-toxic dose of prednisolone (e.g. 10 mg alternate days) may be tried. Other options include intermittent immunoglobulin, cyclophosphamide, azathioprine, danazol, interferon, vincristine and high-dose pulsed dexamethasone. All are associated with isolated successes and there is a large element of 'try it and see' in the management of these patients.

#### DRUG-INDUCED THROMBOCYTOPENIA

Many drugs have been linked with isolated thrombocytopenia. The evidence for causation is often circumstantial. Where the pathogenesis has been explored (e.g. quinine), thrombocytopenia has been caused by anti-platelet antibodies. It is likely that in most cases the antigen is a complex formed between the drug (hapten) and some plasma protein or other carrier molecule. The resultant immune complex attaches to the platelets which (as 'innocent bystanders') are removed from the circulation by the cells of the reticuloendothelial system. A few drugs cause idiosyncratic thrombocytopenia by another process: megakaryocyte suppression (e.g. chlorothiazides) or direct platelet damage (e.g. ristocetin). In immune destruction, thrombocytopenia usually develops within a day and the onset of bleeding can be abrupt and severe. Management is withdrawal of the offending drug and platelet transfusions (or even exchange transfusion) for dangerous bleeding.

#### POST TRANSFUSION PURPURA

In this very rare syndrome severe thrombocytopenia follows a blood transfusion. In most cases the patient's platelets are negative for the platelet antigen  $PL^{A1}$  and the transfused platelets are  $PL^{A1}$  positive. In a way incompletely understood an anti  $PL^{A1}$  isoantibody destroys the patient's own platelets. Thrombocytopenia develops around one week after transfusion and bleeding may be severe. Intravenous immunoglobulin appears to be an effective treatment.

#### Thrombocytopenia

Thrombocytopenia (a low platelet count) is a relatively common laboratory finding. It is important that it is confirmed by inspection of a blood film.

In general thrombocytopenia can be caused by failure of marrow production (e.g. leukaemia), shortened platelet life span (e.g. ITP), sequestration in the spleen and dilution by massive blood transfusion.

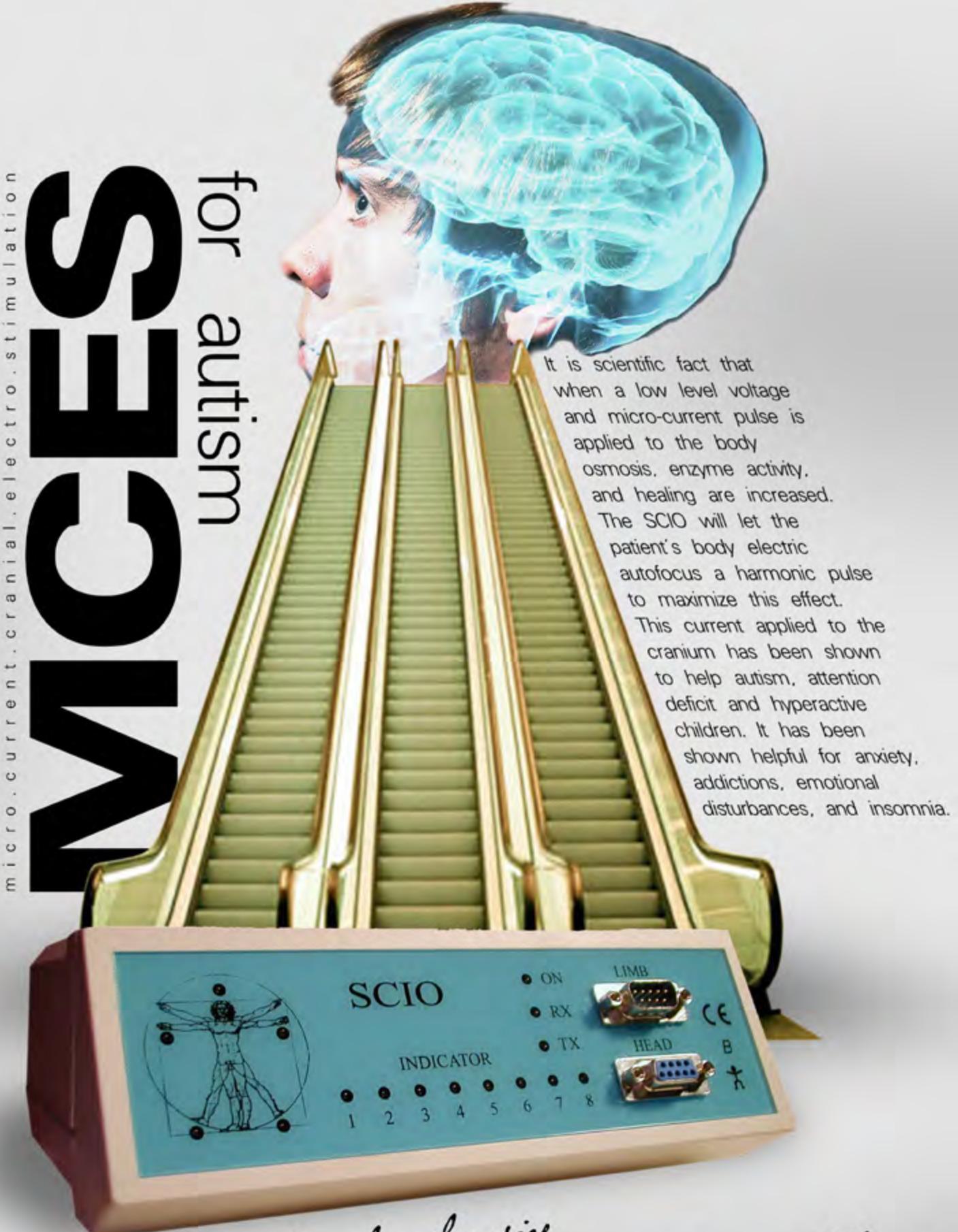
Idiopathic thrombocytopenic purpura (ITP) is a disease characterised by immunological destruction of platelets. Acute ITP is usually seen in childhood and is typically self-limiting. Chronic ITP classically occurs in young women. There is often an initial response to steroid treatment but splenectomy may ultimately be required.

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## DISORDERS OF PLATELET FUNCTION AND VASCULAR PURPURAS

Platelet dysfunction should be considered wherever there are the clinical symptoms and signs of thrombocytopenia in the presence of a normal or only moderately reduced platelet count. Disorders of platelet function can be divided into inherited disorders which are rare but well characterised in the laboratory, and acquired disorders which are much more common but often of obscure aetiology. Bleeding problems may also arise in a number of inherited and acquired disorders of the vasculature and its supporting connective tissue the vascular purpuras.

### LABORATORY TESTING OF PLATELET FUNCTION

A good starting point is a blood count and blood film. Some disorders of platelet function are associated with a change in platelet number and/or size. *The bleeding time* is a useful test of platelet function as it specifically assesses the formation of the platelet plug in a skin wound. A small standard incision is made in the forearm skin and the time to cessation of bleeding recorded (normally 21/2 to 91/2 minutes in the standard template method). A prolonged time is seen in thrombocytopenia and in platelet dysfunction, but the test is a poor predictor of the likelihood of significant haemorrhage.

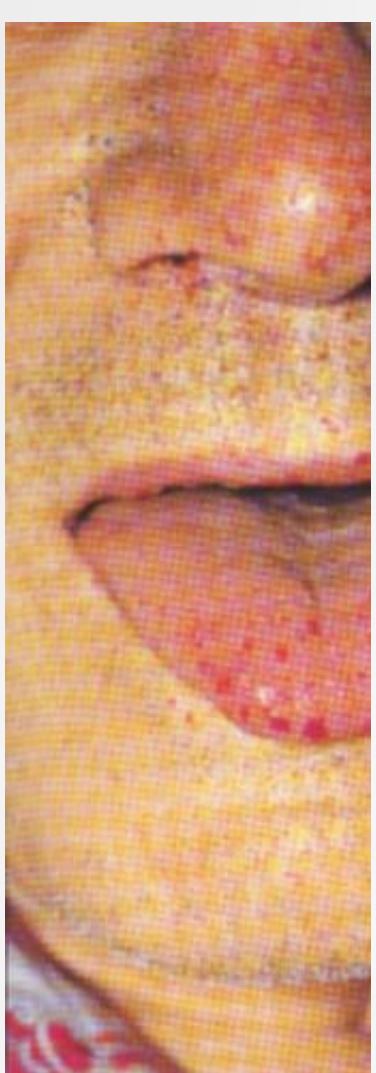


Fig. 1 Senile purpura

Fig. 2 Telangiectasia in hereditary haemorrhagic telangiectasia

*Platelet aggregation studies* assess the ability of platelets to aggregate in response to the addition of a variety of agonists (e.g. ADP, adrenaline, collagen). Disorders of platelet function may cause diminished aggregation responses to one or more of the agonists. Particularly in inherited disorders, the response (or lack of it) to the commonly used agonists has a characteristic pattern (see below).

Other more rarely performed tests include the measurement of platelet surface glycoproteins and platelet granule contents. Ultimately, none of these tests is a substitute for a careful clinical history establishing the nature of any bleeding episodes, drug exposure, and whether there is a family history of bleeding.

### INHERITED DISORDERS OF PLATELET FUNCTION

The commonest inherited platelet function and coagulation disorder, von Willebrand's disease.

#### Bernard Soulier syndrome

This is a rare autosomal recessive bleeding disorder. There is a combination of platelet dysfunction, thrombocytopenia and abnormal platelet morphology. The mild thrombocytopenia is probably caused by reduced platelet survival. The functional platelet defect arises from deficiency of the glycoprotein (GP) Ib-IX complex. This complex is crucial for the initial adhesion of platelets to exposed subendothelium at high shear flow and for binding of platelets to fibrin. In platelet aggregation studies there is failure to aggregate with ristocetin. Bleeding can be severe and particularly complicates other predisposing events such as peptic ulcers and pregnancy. Patients require platelet transfusion for severe bleeding and prior to surgery. DDAVP is useful in some cases.

#### Glanzman's thrombasthenia

This rare autosomal recessive disease is also caused by loss of a platelet glycoprotein - GP IIb-IIIa. This normally acts as a receptor for adhesive proteins such as fibrinogen and von Willebrand factor. Platelet numbers and morphology are normal but the platelets fail to aggregate with all agonists. Clinical manifestations are variable but there is typically onset in the neonatal period and subsequent cutaneous and gastrointestinal bleeding, and menorrhagia. The severity of bleeding often decreases with age. Platelet transfusions are indicated where local haemostatic measures fail.

Table 1 Causes of abnormal platelet function

<b>Inherited</b>	Bernard Soulier syndrome Glanzman's thrombasthenia Storage pool diseases Defects of thromboxane synthesis
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<b>Acquired</b>	Drugs (e.g. aspirin) Foods (e.g. garlic) Chronic renal failure Cardiopulmonary bypass surgery Blood diseases acute myeloid leukaemia myelodysplastic syndromes myeloproliferative disorders myeloma Various systemic disorders' These include disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP).
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#### Other disorders

Hereditary diseases of platelet function may also result from deficiency of platelet storage organelles (storage pool diseases) or an enzyme defect in thromboxane synthesis. In general these syndromes only cause mild bleeding problems.

#### ACQUIRED DISORDERS OF PLATELET FUNCTION

These disorders are common. Causes include foods, drugs, systemic disorders and diseases of the blood.

##### Aspirin

Many drugs can affect platelet function but aspirin is the best documented and the most frequently prescribed. Aspirin acetylates and irreversibly inactivates the enzyme cyclooxygenase, preventing the production of thromboxane A<sub>2</sub> from arachidonic acid and inhibiting aggregation for the remainder of the platelet's lifespan. Even small doses of aspirin can dramatically prolong the bleeding time and cause haemorrhage in patients with thrombocytopenia or other co-existent bleeding problems.

##### Chronic renal failure

Uraemia can lead to multiple platelet defects. Abnormal platelet aggregation does not correlate well with the severity of renal failure but there may be improvement after dialysis. The nature of bleeding in chronic renal failure is consistent with abnormal platelet function. Epistaxis, gastrointestinal haemorrhage and menorrhagia are common problems. Treatment of the underlying renal disease (e.g. dialysis, transplantation) may need to be supplemented with platelet transfusions and DDAVP.

##### Cardiopulmonary bypass

During and immediately after cardiopulmonary bypass surgery platelet aggregation is decreased, the contents of platelet granules reduced and the bleeding time is longer than would be expected for the degree of thrombocytopenia. Excessive bleeding is uncommon but where this happens platelet transfusion is efficacious.

##### Haematological diseases

Platelet function is impaired in a number of blood diseases, including acute myeloid leukaemia, myelodysplastic syndromes, myeloproliferative disorders and myeloma.

#### VASCULAR PURPURAS

A bleeding tendency caused by a local or general vascular abnormality is referred to as a vascular purpura. Diagnosis of these diseases is made mainly on clinical grounds with laboratory exclusion of other haemostatic defects.

##### Inherited disorders

###### Hereditary haemorrhagic telangiectasia (HHT)

The hallmark of this autosomal dominant disease is the development of small, thinwalled venous angiomas in the skin, mucous membranes and other organs. The characteristic telangiectasia make this relatively rare disease a common occurrence in medical examinations. Clinical problems include recurrent epistaxis (90% of cases), gastrointestinal haemorrhage, haematuria and pulmonary arteriovenous malformations (PAVMs). Chronic bleeding from the gut causes iron deficiency anaemia. Management includes local control of bleeding (e.g. laser treatment of telangiectasia), iron supplements and embolisation of PAVMs. Recent research has identified a putative HHT gene abnormality located at 9q34.

**Inherited diseases of connective tissue** Several rare inherited disorders of connective tissue predispose to bleeding. The mechanism is either a general failure of support of blood vessels or defective interaction between platelets and abnormal collagen. Specific diseases include Ehlers-Danlos syndrome, pseudoxanthoma elasticum and Marfan's syndrome.

##### Acquired disorders

This is a very heterogeneous group. Henoch-Schönlein purpura is a syndrome usually seen in childhood where an itchy purpuric rash typically follows an infection. Spontaneous remission is the rule but renal failure may result. Other causes of acquired purpuric rashes include a range of infections, drug reactions, scurvy, trauma, prolonged steroid therapy and simple old age (senile purpura).

##### Disorders of platelet function and vascular purpuras

Platelet dysfunction should be considered where there are the clinical features of thrombocytopenia in the presence of a normal or only moderately reduced platelet count.

Laboratory testing of platelet function normally includes a blood count, a blood film, a bleeding time and platelet aggregation studies.

Inherited disorders of platelet function are generally well characterised but rare (e.g. Bernard Soulier syndrome), whereas acquired disorders are more frequent but often of obscure aetiology.

Aspirin is a common cause of acquired platelet dysfunction.

A 'vascular purpura' is a disorder with a bleeding tendency caused by a local or general vascular abnormality. Diseases may be inherited (e.g. hereditary haemorrhagic telangiectasia) or acquired (e.g. Henoch-Schönlein purpura).



## HAEMOPHILIA

Haemophilia is an inherited disorder of coagulation. The general term haemophilia is usually taken to mean haemophilia A, a deficiency of factor VIII, but a smaller number of cases are caused by a deficiency of factor IX (haemophilia B).

**Fig. 1 a, b** Chronic knee damage in severe haemophilia A

### HAEMOPHILIA A

Haemophilia A is transmitted as an X-linked recessive disorder. Thus, all males with the defective gene have haemophilia, all sons of haemophiliac men are normal, all daughters are obligatory carriers and daughters of carriers have a 50% chance of also being carriers. The disease affects one in every 8000 males. The gene for factor VIII is situated at the tip of the long arm of the X chromosome. A wide variety of mutations of the gene can lead to underproduction of factor VIII and the clinical syndrome of haemophilia. In 50% of haemophilia families an unusual molecular genetic abnormality involving inversion of the factor VIII gene has been found. A family history is not inevitably present, as up to 30% of all new cases of haemophilia are due to recent sporadic mutations.

### CLINICAL FEATURES

As factor VIII is a critical component of the blood coagulation pathway, low levels predispose to recurrent bleeding. The likelihood of bleeding can be roughly predicted from the factor VIII level. Clinical features can be divided into those attributable to bleeding and those arising from complications of treatment.

#### Bleeding in haemophilia

The disease usually becomes apparent when the child begins to crawl. Severely affected patients experience 30-50 bleeding episodes each year. The most common problems are spontaneous bleeds into joints, often elbows or knees, although any joint can be involved. Patients may develop particular *target joints* which bleed frequently. They often have an innate feeling that a bleed has started prior to any objective signs. Recurrent or inadequately managed joint bleeds lead to chronic deformity of the joint with swelling and pain. Bleeding may also afflict deep-seated muscles, often the flexor muscle groups. If ignored, the enlarging haematoma can compress adjacent nerves and vessels with serious consequences. Haematuria is not unusual and, until recently, intracranial bleeding was the most common cause of death in haemophilia.

#### Complications of treatment

In affluent countries, factor VIII replacement treatment as described below has been enormously beneficial in allowing early control of bleeding and the avoidance of chronic joint damage. Unfortunately, most haemophiliacs (over 70% of severe cases) treated before 1985 have become infected with pathogenic viruses contaminating factor VIII concentrate, notably HIV and hepatitis C. HIV infection remains asymptomatic for long periods in a significant minority, but most patients eventually develop acquired immunodeficiency syndrome. Kaposi's sarcoma is, however, very rare. The full implications of hepatitis C infection are not fully understood but end-stage liver disease or hepatocellular carcinoma may result.

### DIAGNOSIS

Haemophilia is associated with a prolonged activated partial thromboplastin time (APTT) in the routine clotting screen. The diagnosis is confirmed by a factor VIII clotting assay. In the presence of a family history there are usually few problems in identifying the disorder. Tests can be performed on cord blood. In the absence of a family history the disease may present in a young child with bruising and a swollen joint and be mistakenly regarded as non-accidental injury. Mild haemophilia may only cause problems after trauma or surgery. All patients with bleeding or bruising of a severity disproportionate to the trauma sustained should be investigated to exclude a bleeding disorder.

### MANAGEMENT

Treatment of haemophilia is complex, and severe disease is best managed in haemophilia centres where an experienced team of doctors, nurses, physiotherapists and social workers can help patients and their families to lead a relatively normal life.

#### Treatment of bleeding

Most haemophiliacs require replacement therapy with factor VIII concentrate and this is usually self-administered at home when a bleed occurs ('on demand' treatment). The dose and duration of treatment depends on the patient's size and the locality and magnitude of the bleed. One unit of factor VIII is the amount contained in 1 ml of normal plasma. For spontaneous haemarthroses it is sufficient to raise the factor VIII level to 30% of normal; in a 70 kg man this entails a dose of around 1000 units. More serious bleeding or surgery requires levels of 70-100% maintained until the risk subsides (Fig. 3). The factor VIII products used are increasingly high purity with low levels of protein contamination and recombinant factor VIII is now entering clinical practice. The availability of safe affordable genetically engineered recombinant factor VIII allows prophylactic (thrice weekly) treatment in children with eradication of bleeding and improved quality of life. An annoying complication of factor VIII treatment is the development of antibodies to factor VIII (inhibitors) in 10-15% of patients. Treatment of such patients is highly specialized. Strategies include the use of porcine factor VIII, factor IX and activated factor IX concentrates (e.g. FEIBA).

In patients with mild disease (factor VIII greater than 10%) 1-amino-8-D-arginine vasopressin (DDAVP), given intravenously or inhaled as snuff, mobilises factor VIII from stores and may avoid the need for concentrate. The

antifibrinolytic agent tranexamic acid can also, be used to reduce bleeding and thus the requirement for factor VIII - it should, however, be avoided in haematuria where it can induce clot colic.

#### **The carrier state and genetic counseling**

Female carriers are generally asymptomatic but some will have low enough levels of factor VIII (10-30%) to cause excessive bleeding after trauma. In families with inversion of the X-chromosome (see above), relatively simple molecular biology methods are used in carrier and pre-natal diagnosis (Fig. 4). In other families identification of the mutation requires more advanced techniques and here carrier and pre-natal diagnosis often depends on the detection of DNA polymorphisms which act as indirect markers of the factor VIII gene.

#### **HAEMOPHILIA B**

Haemophilia B is an X-linked recessive bleeding disorder in which there is a deficiency of factor IX. The incidence is approximately 3-4 per 100000 male births. There are many clinical similarities to haemophilia A severely affected patients suffer recurrent spontaneous joint bleeds. However, inhibitors (antibodies to factor IX) are less common than in haemophilia A, and the incidence of HIV infection may be different depending on the historical source of factor IX. Earlier factor IX concentrates were associated with thrombo-embolic complications but safer high purity preparations are now available for treatment. The half-life of infused factor IX is around 24 hours and thus it can often be given just once daily to maintain levels after spontaneous bleeding or surgery.

#### **Treatment of viral infection**

Haemophiliacs with HIV infection require state of the art management of the physical and social problems which can arise. Treatment of hepatitis C infection is contentious but alpha interferon does lead to at least short-term improvement of liver disease in a minority of cases.

#### **Haemophilia**

Haemophilia A is an X-linked recessive disorder characterised by deficiency of factor VIII. Severely affected patients suffer recurrent spontaneous bleeds, most often into joints. Replacement therapy with factor VIII concentrate is needed in all but mild cases; previous contamination of concentrates has led to HIV and hepatitis C infection. DDAVP and tranexamic acid can help control bleeding in mild disease. The management of choice in severely affected children is prophylactic treatment with genetically engineered recombinant factor VIII.

Haemophilia B is characterised by deficiency of factor IX; inheritance and clinical features are similar to haemophilia A.

#### **VON WILLEBRAND'S DISEASE AND OTHER INHERITED COAGULATION DISORDERS**

##### **VON WILLEBRAND'S DISEASE**

Von Willebrand's disease (VWD) is the most common inherited bleeding disorder. Approximately 125 people per million have symptomatic VWD and asymptomatic deficiencies in von Willebrand factor (VWF) are detectable in nearly 1% of the general population. All VWD is caused by mutations in the gene for VWF. VWF is an adhesive glycoprotein secreted by endothelium and megakaryocytes. It is a multimeric protein with a characteristic normal distribution of multimer sizes in plasma. VWF has two key functions: promotion of platelet adhesion to damaged endothelium and other platelets (Fig. 1) and the transport and stabilisation of factor VIII. Thus, the clinical disorder of VWD is associated with excessive bleeding due to abnormal platelet function and low factor VIII activity. The clinical and laboratory heterogeneity of VWD necessitates the definition of several subtypes. Recently the classification has been simplified by focusing on the phenotype of the VWF protein (i.e. 'multimer pattern') in patient plasma and platelets.

##### **CLASSIFICATION**

The current classification of VWD depends on electrophoretic analysis of VWF multimers. In type I VWD, the multimers appear to be normal in structure and function but decreased in concentration. In type 2 VWD there is a qualitative deficiency of VWF divisible into four subtypes. In type 2A there is an absence of high molecular weight VWF multimers and markedly reduced VWF binding to platelets. 2B refers to a variant where defective platelet adhesion results, paradoxically, from increased binding of VWF to platelets. In 2M there is decreased platelet-dependent VWF function despite a relatively normal multimer pattern whilst 2N is characterised by failure of VWF to bind factor VIII. In the rare type 3 form, there is an almost complete deficiency of VWF and the factor VIII level is markedly decreased. Although this may seem complicated, it represents a considerable simplification with only six diagnostic categories compared with around thirty previously. There is correlation between the subtype and the mode of inheritance. Type I VWD is the most common form of the disease (80% of cases) and inheritance is often autosomal dominant. Type 2 VWD (15% of cases) may be dominant or recessive and the type 3 variant is recessive. Because inherited deficiencies of VWF function are common the accidental co-inheritance of otherwise recessive VWD alleles may occur ('compound heterozygosity'). At the molecular level, quantitative deficiencies correlate with promoter, nonsense, and frame shift mutations and with large deletions. Qualitative deficiencies tend to be seen with missense mutations and small in-frame deletions or insertions.

##### **CLINICAL FEATURES**

Severe VWD is characterised by spontaneous bleeding, particularly epistaxes, gum bleeding and menorrhagia. Easy bruising is also common but (with the exception of type 3) haemarthroses and muscle haematomas are rare. Milder disease often presents with excessive bleeding following trauma or surgical procedures and the diagnosis can easily be missed. A thorough history is crucial and must include assessment of the severity of recent bleeding, the existence of previous bleeding pro Diems (particularly after surgery and dental extractions) and the presence of a family history of easy bleeding. Death from bleeding is rare but it may follow massive gastrointestinal haemorrhage.

##### **Table 1 Summary of classification of VWD**

Type 1 VWD is a partial quantitative deficiency of VWF

Type 2 VWD is a qualitative deficiency of VWF

Type 3 VWD is a virtually complete deficiency of VWF

Type 2A VWD is a qualitative variant with an absence of high molecular weight VWF multimers

Type 2B VWD is a qualitative variant with *Increased* affinity of VWF for platelet glycoprotein 1b (reduced in other types)

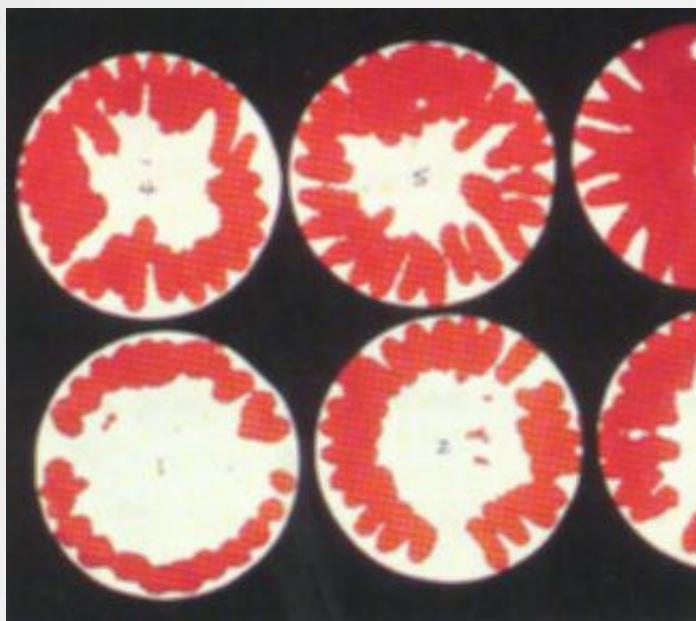
Type 2M VWD is a qualitative variant not caused by absence of high molecular weight multimers

Type 2N VWD is a qualitative variant with reduced affinity of VWF for factor VIII

Note: mixed phenotypes may be caused by compound heterozygosity,

## LABORATORY DIAGNOSIS

The diagnosis of classic type I VWD is usually straightforward but recognition of milder forms and rarer variants can be difficult and the following tests may have to be repeated several times before a final conclusion is reached.



**Fig. 1** Prolonged bleeding time in VWD. There is a significant bleeding onto the applied filter paper.

## OTHER INHERITED COAGULATION DISORDERS FACTOR DEFICIENCIES

### Factor VIII and factor IX deficiencies

#### Factor XI deficiency

This bleeding disorder is almost entirely confined to Ashkenazi Jews. Inheritance is via an incompletely recessive autosomal gene and homozygous patients have very low factor XI levels (less than 5% of normal). Factor XI concentrate is the treatment of choice in significant bleeding.

#### Factor VII deficiency

This is inherited as an autosomal recessive disorder. Homozygotes can have all the bleeding problems seen in haemophilia. The diagnosis is confirmed by factor VII assay and factor VII concentrate is available for treatment.

#### Factor V deficiency

In this rare autosomal recessive disease the severity of bleeding is more dependent on the patient's platelet factor V level than the plasma concentration of factor V.

#### Factor XIII deficiency

Another rare autosomal recessive disorder, factor XIII deficiency causes a severe haemorrhagic tendency and poor wound healing. Most sufferers present early in life, often with profuse bleeding from the umbilical cord, and death may result from intracranial haemorrhage. Screening coagulation tests are normal. Diagnosis requires the laboratory demonstration of solubility of patient plasma clots in urea 5M (there is defective cross-linking of fibrin). Factor XIII concentrate is available for treatment.

## ABNORMALITIES OF FIBRINOGEN

Inherited disorders of fibrinogen are broadly divisible into quantitative deficiencies (apofibrinogenaemia and hypofibrinogenaemia) and qualitative abnormalities (dysfibrinogenaemia). Apofibrinogenaemia is an autosomal recessive disease in which blood fails to clot in all coagulation screening tests and plasma fibrinogen is barely detectable by radioimmunoassay. The bleeding tendency can be severe with spontaneous haemorrhage and excessive blood loss after surgery. Hypofibrinogenaemia is a less well-defined entity with milder bleeding problems. The dysfibrinogenaemias are a heterogeneous group of rare autosomal dominant disorders. Patients may have a haemorrhagic disorder or, paradoxically, an increased risk of thrombosis.

**Blood count.** The platelet count is normal except for a moderate reduction in some cases of type 2B disease.

**Activated partial thromboplastin time (APTT).** Usually prolonged due to low Factor VIII: C levels. The prothrombin time (PT) is normal.

**Bleeding time.** Generally prolonged due to platelet dysfunction but may be normal in mild disease.

**Factor VIII: C assay.** Often low. May be borderline or normal in mild type 1 disease.

**VWF antigen.** Reduced in most cases.

**Ristocetin cofactor activity.** Reduced in most cases. Probably the best laboratory indicator of disease severity.

**Platelet aggregation studies.** Ristocetin (an obsolete antibiotic) induces platelet aggregation in normal plasma but not in severe VWD. An exception is the type 2B variant where platelets aggregate at unusually low concentrations of ristocetin.

**Multimer analysis.** The multimer composition of circulating VWF is assessed by either crossed immunoelectrophoresis or sodium dodecyl sulphate electrophoresis.

## MANAGEMENT

Very mild bleeding problems may require little intervention, perhaps just local measures and the prescription of an antifibrinolytic drug such as tranexamic acid. More significant bleeding generally responds to an infusion of DDAVP which stimulates release of VWF from stores. DDAVP is predictably most effective in patients with a partial quantitative impairment of VWF (type 1). It is less effective in most type 2 variants and is possibly contraindicated in type 2B where it may exacerbate bleeding by inducing thrombocytopenia. Patients with type 3 disease do not respond to DDAVP as they lack any capacity to secrete VWF. Where DDAVP is ineffective or contraindicated, then intermediate purity factor VIII concentrates, containing both VWF and factor VIII, are used. An unusually sustained rise in factor VIII levels can be obtained as the VWF in the concentrate prolongs survival of the patient's own factor VIII. Patients with VWD normally require treatment with either DDAVP or factor VIII concentrate prior to surgery. Effective genetic counseling in VWD demands a full understanding of the disease subtype and mode of inheritance. Advice may be completely different classical dominant type I disease and other subtypes or cases of compound heterozygosity.

## Von Willebrand's disease and other inherited coagulation disorders

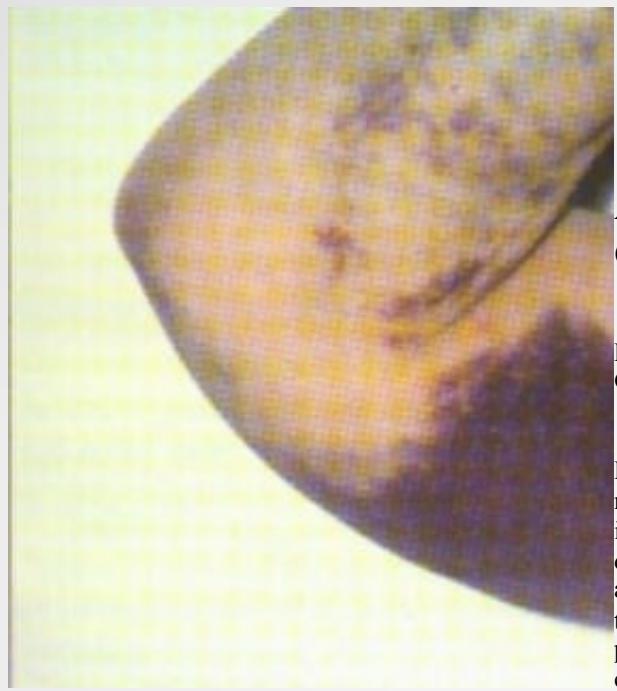
VWD is a relatively common and very heterogeneous inherited bleeding disorder. Deficiency of Von Willebrand factor (VWF) causes abnormal platelet function and low factor VIII activity.

Classification of VWD relies on electrophoretic analysis of VWF multimers.

Mild bleeding problems in VWD require little intervention. More significant bleeding is treated with either DDAVP or intermediate purity factor VIII concentrates.

There are various other inherited coagulation factor deficiencies. In most there are specific concentrates available for treatment.

Inherited disorders of fibrinogen include quantitative deficiencies (apofibrinogenaemia and hypofibrinogenaemia) and qualitative abnormalities (dysfibrinogenaemia).



## ACQUIRED DISORDERS OF COAGULATION

### DISSEMINATED COAGULATION (DIC)

DIC is a complex clinical syndrome which complicates many serious illnesses (Table 1). It is characterised by intravascular deposition of fibrin and accelerated degradation of fibrin and fibrinogen caused by excess activity of proteases, notably thrombin and plasmin, in the blood. DIC is heterogeneous both in its pathophysiology and clinical manifestations. In most cases it probably begins when circulating blood is exposed to tissue factor released from damaged tissues, malignant cells or injured endothelium. This in turn leads to generation of thrombin which causes formation of soluble fibrin, activation of circulating platelets, and secondary fibrinolysis. Figure 1 attempts to summarise the multiple mechanisms at work.

**Fig. 1** Spontaneous bruising in acquired haemophilia.

DIC can cause bleeding, large vessel thrombosis and haemorrhagic tissue necrosis. The coagulation defect arises from consumption of coagulation factors and platelets and increased fibrinolytic activity. In clinical practice acute DIC usually presents as widespread bleeding in an ill patient. Oozing of blood from cannulation sites is characteristic. Microthrombus formation can lead to irreversible organ damage; the kidney, lungs and brain are frequent targets. DIC is not necessarily a fulminant syndrome, more chronic forms may be seen particularly in association with malignancy (e.g. prostatic carcinoma).

Diagnosis depends on the laboratory demonstration of accelerated fibrinolysis accompanied by falling levels of coagulation factors in a patient with a disease known to cause DIC. The following combination of laboratory test abnormalities is typical:

Reduced platelet count.

Prothrombin time prolonged and activated partial thromboplastin time (APTT) usually prolonged.

Thrombin time prolonged.

Fibrinogen level reduced.

High levels of fibrinogen degradation products (FDPS) and cross-linked fibrin degradation products ('D-Dimers'). The cornerstone of management of DIC is the treatment of the underlying disease. Patients are more likely to die from the underlying disease than from thrombosis or bleeding. However, specific treatment of DIC may be life-saving and if bleeding occurs support with blood products is indicated. Platelets, fresh frozen plasma (FFP - a source of coagulation factors) and cryoprecipitate (a source of fibrinogen) may all be used. Wherever possible the choice of blood products should be guided by the platelet count and coagulation tests. Much more controversial is the use of pharmacological inhibitors of coagulation and fibrinolysis. Although heparin can reduce clotting factor consumption and secondary fibrinolysis, it can also increase the haemorrhagic risk by its anticoagulant action. Antifibrinolytic drugs (such as tranexamic acid) are generally contraindicated because of their thrombotic risk.

### Table 1 Common causes of DIC

Infections - particularly septicaemia

Malignancy - disseminated carcinoma or acute leukaemia

Obstetric emergencies - septic abortion, abruptio placentae

### INTRAVASCULAR

Shock - surgical trauma, burns  
Severe haemolytic transfusion reaction  
Liver disease

### VITAMIN K DEFICIENCY

Vitamin K in the body is derived from dietary vegetables and intestinal flora. Once absorbed it is stored in the liver and following further metabolism it acts as a cofactor for 7-glutamyl carboxylation of coagulation factors II, VII, IX, and X and proteins C and S. Vitamin K deficiency is probably the most common acquired coagulation disorder encountered in hospital patients. The vitamin K antagonist effect of warfarin is discussed and the vitamin K deficiency of liver disease later in this section.

#### Dietary deficiency

Normal dietary requirements for vitamin K are low (0.1-0.5 g/kg) and thus patients must be considerably malnourished before overt deficiency occurs. This most commonly occurs in patients receiving intensive medical care, particularly where broad spectrum antibiotics are used. Deficiency is suggested clinically by excessive bleeding and in the laboratory by a prolonged prothrombin time. Supplemental vitamin K should ideally be given before bleeding problems occur.

#### Malabsorption

Malabsorptive conditions such as coeliac disease and tropical sprue may lead to vitamin K deficiency. Vitamin K can also be lost in chronic biliary obstruction due to failure of bile salts necessary for fat absorption to reach the bowel.

#### Haemorrhagic disease of the newborn

Vitamin K deficiency may arise in the first weeks of life, most commonly in breast-fed, full-term and otherwise healthy babies. Contributory factors include low placental transfer of vitamin K, low concentrations of vitamin K in breast milk, low intake of milk and a sterile gut. Haemorrhage most commonly occurs on the 2<sup>nd</sup> to 4<sup>th</sup> day. A coagulation screen is abnormal with the prothrombin time and APTT both prolonged. In most countries prophylactic vitamin K (1mg intramuscular injection) is given to newborn babies. Affected babies respond to parenteral vitamin K but fresh frozen plasma may be needed for severe haemorrhage.

### LIVER DISEASE

The liver is vital to normal haemostasis. It produces all the factors of the intrinsic and extrinsic coagulation pathway and clears potentially damaging products of coagulation such as fibrin degradation products and activated clotting factors. Thus, in advanced liver disease there are often multiple haemostatic abnormalities including reduced synthesis of clotting factors, increased consumption of clotting factors (DIC), qualitative and quantitative platelet abnormalities, qualitative fibrinogen abnormalities and accelerated clot lysis. Where bleeding occurs, the type of therapy is guided by the dominant haemostatic problems. Possible interventions include parenteral vitamin K, fresh frozen plasma, cryoprecipitate and platelet infusions.

### ACQUIRED HAEMOPHILIA

Antibodies ('inhibitors') that block the action of coagulation factors may appear in patients who have no hereditary disorder of coagulation. Such autoantibodies most commonly target factor VIII and the clinical syndrome is termed 'acquired haemophilia'. Acquired haemophilia may be associated with a number of conditions including rheumatoid arthritis and other autoimmune disorders, skin disorders, drug therapy (particularly penicillin), pregnancy and the puerperium. However, the most common presentation is in an elderly patient (greater than 60 years) with no associated condition. Possible clinical problems include haemorrhage into soft tissues and muscles, haematuria,

haematemesis and prolonged bleeding postpartum or postoperatively. Bleeding can be difficult to control and death occurs in 10-20% of cases.

In the laboratory, the diagnosis of acquired haemophilia is suggested by a prolonged APTT worsening with incubation and not corrected by the addition of normal plasma, and a low factor VIII level. Laboratory assay of the inhibitor is based on the ability of the patient's plasma to neutralise the activity of a known amount of factor VIII. Management is complex but can be divided into the treatment of the acute bleeding episode and subsequent attempts to eliminate the autoantibody by immunosuppressive treatment.

Possible approaches to the acute episode include large doses of human factor VIII concentrate, porcine factor VIII, prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant factor VIIa. Immunosuppressive strategies include intravenous immunoglobulin and plasma-pharesis in the acute episode and longer-term steroids or cyclophosphamide. Many elements of management remain controversial.

#### Acquired disorders of coagulation

Disseminated intravascular coagulation (DIC) is a complex clinical syndrome which complicates serious illness. It causes both haemorrhage and thrombosis. Laboratory tests are needed and monitor to confirm the diagnosis. Treatment of DIC is essentially that of the underlying cause. Blood products are often indicated where bleeding occurs.

Vitamin K deficiency is a common acquired coagulation disorder.

Advanced liver disease can cause multiple haemostatic abnormalities.

Acquired haemophilia is generally caused by an autoantibody targeted against factor VIII. It may be idiopathic or associated with other autoimmune diseases, pregnancy or drug treatment.

PCC, prothrombin Complex concentrated a, activated, Ig, immunoglobulin.

#### THROMBOPHILIA

Patients who are predisposed to thrombosis generally either have a disorder of the blood or an abnormality of the vessel wall. Where enhanced coagulation is the major mechanism, the disorder is referred to as 'thrombophilia'. Patients with thrombophilia either tend to have thrombosis at an unusually early age or to develop recurrent thrombotic problems. Venous thrombosis predominates with the chance of thrombosis increased by the coexistence of other risk factors such as obesity, surgery, pregnancy and malignancy. Thrombophilia can be inherited or acquired.

Table 1 Characteristics suggesting possibility of thrombophilia

Venous thrombosis in patient less than 40 years old  
Recurrent venous thrombosis or thrombophlebitis  
Venous thrombosis in unusual site (e.g. axillary vein)  
Arterial thrombosis in patient less than 30 years old  
Strong family history of venous thrombosis  
Recurrent fetal loss  
Skin necrosis in patient receiving warfarin

Table 2 Major risk factors for thrombosis

Venous	Arterial	
Immobility		Smoking
Obesity	Male sex	
Oral contraceptive pill		Hypertension
Trauma/surgery		Strong family history
Thrombophilia (see text)		Hyperlipidaemia
Pregnancy		Diabetes mellitus
Malignancy		Raised fibrinogen
Increasing age		Increasing age

#### WHICH PATIENTS SHOULD BE INVESTIGATED FOR THROMBOPHILIA?

Table I summarises factors which should prompt consideration of thrombophilia. Accurate history taking is essential; particular attention should be given to the nature of the recent thrombotic event, the presence of known risk factors (Table 2), a previous history of thrombosis and the family history.

Definition of a 'positive' family history of thrombosis is problematic. If we use the simple definition of a history of deep vein thrombosis (DVT) or pulmonary embolus (PE) in a first or second degree relative, then approximately 25% of all patients will have a positive family history. Even amongst those with a strong family history only a small minority will have a cause of thrombophilia identified.

Basic investigations of thrombophilia should include a blood count (to exclude polycythaemia and other myeloproliferative disorders) and a basic coagulation screen (prothrombin time, activated partial thromboplastin time, and thrombin time or fibrinogen). Further laboratory testing is dictated by the possible causes of familial and acquired thrombophilia detailed below. Testing for thrombophilia should not be undertaken during an acute episode of venous thromboembolism when low levels of coagulation inhibitors are routinely found. It must also be remembered that systemic disorders such as liver disease or disseminated intravascular coagulation (DIC) can depress the levels of coagulation inhibitors and thus simulate the laboratory abnormalities found in familial thrombophilia.

#### FAMILIAL THROMBOPHILIA

In theory, familial thrombophilia could be caused by any genetically determined defect of the coagulation or fibrinolytic systems that causes accelerated thrombin formation or impaired fibrin dissolution. In practice, the well-defined causes are associated with accelerated thrombin formation either due to a shortage or failure of activation of one of a number of circulating inhibitors of coagulation.

#### Resistance to activated protein C (APCR)

The anticoagulant property of activated protein C (APC) lies in its capacity to inactivate the activated cofactors Va and VIII, by limited proteolysis. Recent studies have shown that inherited resistance to the anticoagulant action of APC is an important cause of thrombophilia. In most cases resistance is caused by a single point mutation in the factor V gene (factor V Leiden) with replacement of Arg<sub>506</sub> with Gln. Arg<sub>506</sub> is located at one of the APC cleavage sites in factor V and the mutated V is less sensitive than normal V to APC mediated inactivation. APCR has an autosomal dominant mode of inheritance and is the most common known cause of familial thrombophilia. The increased risk of venous thrombosis in APCR has been estimated as 5-10 fold in heterozygotes and 50-100 fold in homozygotes. The prevalence of the disorder in Western Europe is 3-7% with an incidence of around 20% in unselected cases of venous thrombosis. In practice, the risk of venous thrombosis is highest in patients homozygous for the mutation or in heterozygotes with other risk factors (Table 2). It is not yet clear if APCR is associated with an increased risk of arterial thrombosis.

Fig. 1 **Actions of proteins C and S.** Thrombin and protein C bind to thrombomodulin (TM), an endothelial membrane protein (steps 1 and 2). Protein S then binds to this complex and also endothelial phospholipid (PL) (step 3). The resulting complex proteolytically degrades activated factors V and VIII (step 4). Protein C is activated by proteolytic cleavage by thrombin. In APCR, factor V is relatively resistant to inactivation by the protein C complex.

#### Protein C deficiency

Hereditary deficiency of protein C is an autosomal dominant disorder found in 2-5% of patients with thromboembolic disease. Heterozygotes have protein C levels approximately 50% of normal. It is worth noting that an acquired deficiency of protein C can occur in liver disease, DIC and warfarin treatment. Familial protein C deficiency manifests as an increased incidence of venous thromboembolism. Thrombotic events vary from a superficial thrombophlebitis to DVT and PE. They may be spontaneous or triggered by other factors such as surgery or pregnancy. As in other forms of thrombophilia, the first episode of thrombosis may occur at an early age and then be followed by frequent recurrences. In the rare homozygous form of the disease, the infant can be born with undetectable levels of protein C and quickly develop DIC and skin necrosis due to microvascular thrombosis of subcutaneous vessels (purpura fulminans).

#### Protein S deficiency

Protein S is the non-enzymatic cofactor of protein C. Hereditary deficiency is found in 4-8% of patients presenting with venous thrombosis. Deficiency may be acquired in a variety of diseases and in pregnancy. The clinical manifestations of hereditary protein S deficiency are the same as in protein C deficiency.

#### Antithrombin III deficiency

Antithrombin III (AT III) is the major physiological inhibitor of thrombin and clotting factors IX<sub>a</sub>, X<sub>a</sub>, XI<sub>a</sub> and XII<sub>a</sub>. Deficiency can be inherited in an autosomal dominant manner. Its prevalence is unclear but AT III deficiency probably contributes to venous thrombosis in around 2-5% of younger patients. There are several disease subtypes based on the results of functional and immunological assays; the risk of thrombosis varies between subtypes being greater for an abnormality affecting the reactive (thrombin binding) site than for an abnormality affecting the heparin binding site. Overall, it seems that the risk of venous thrombosis is larger in heterozygotes for AT III deficiency than for those with APCR, protein C or protein S deficiency. The risk increases with age, with up to 80% of patients developing venous thrombosis by 55 years. The relationship between AT III deficiency and arterial thrombosis is uncertain.

#### Other possible forms of familial thrombophilia

High factor VIII concentrations have been associated with an increased risk of venous thrombosis. The mechanisms involved and the degree to which they are genetically determined has still to be elucidated. Other candidates for familial thrombophilia status include the dysfibrinogenaemias and factor XII deficiency.

#### Management of familial thrombophilia

##### Acute venous thrombosis

This should be treated with heparin and warfarin. Patients with AT III deficiency may require unusually high doses of heparin. Warfarin should be continued for at least 3 months. Patients with protein C (and occasionally protein S) deficiency can develop warfarin associated skin necrosis; this may be caused by an initial rapid fall in protein C levels after warfarin commencement leading to a hypercoagulable state and thrombosis in the subcutaneous circulation. The risk can be minimised by ensuring full heparinisation and then introducing warfarin gradually. Protein C concentrates have been given to treat purpura fulminans in homozygous disease.

##### Other situations

In patients with recurrent venous thrombosis, long-term oral anticoagulation with warfarin will often be indicated. This approach is, however, not usually appropriate where this is only a family history of thrombosis with no personal thrombotic events. A possible exception is AT III deficiency where the risk of thrombosis in older patients appears considerable. The management of thrombophilia in pregnancy is particularly complex. Warfarin is potentially teratogenic and subcutaneous heparin is normally the mainstay of treatment. AT III concentrate is available and may be helpful in deficient patients at time of delivery.

##### Counseling

Counseling is frequently not straightforward. Any doubts relating to diagnosis and the probability of thrombosis in asymptomatic family members must be acknowledged. Known risk factors such as immobility, obesity and the oestrogen-containing oral contraceptive should be avoided wherever possible. Recent studies have shown a two to four times increased risk of venous thromboembolism in women receiving hormone replacement therapy (HRT).

#### ACQUIRED FORMS OF THROMBOPHILIA

##### Antiphospholipid antibody syndrome

The definition of antiphospholipid antibody syndrome is imprecise, but diagnosis essentially requires a combination of characteristic clinical events and laboratory identification of an antiphospholipid antibody (Table 3). The syndrome can be 'primary' where the patient has no obvious autoimmune disease or 'secondary' if the patient also has systemic lupus erythematosus (SLE) or a lupus-like disease. About half of all patients have the primary form of the disorder. Up to 2% of the general population have detectable antiphospholipid antibodies - the probability of clinical problems is greatest where the antibody titre is high.

The cause of thrombophilia in antiphospholipid antibody syndrome is not understood. It is possible that the antiphospholipid antibody is merely a marker for an underlying abnormality of coagulation proteins, platelets or endothelial cells. Management is controversial. Where there has been an episode of major thrombosis, warfarin appears to offer the best protection against recurrent thrombosis. It is uncertain if aspirin gives additional benefit. In women with a history of recurrent spontaneous abortion there is no consensus as to best treatment; most studies have focused on aspirin and/or heparin with inconclusive results.

##### Other acquired forms of thrombophilia

In addition to the well established risk factors (Table 2), there are other acquired disorders predisposing to thrombosis. Myeloproliferative disorders are discussed elsewhere. Recent studies have suggested that increased levels of plasma fibrinogen, von Willebrand factor and tissue plasminogen activator (t-PA) are predictors for coronary artery disease. Whether these abnormalities are constitutional changes predisposing to coronary atherosclerosis and thrombosis or whether they are markers of preexisting inflammation and endothelial dysfunction is currently unclear.

Table 3 Antiphospholipid antibody syndrome

#### Clinical features

Recurrent venous and arterial thrombosis  
Recurrent fetal loss  
Immune thrombocytopenia  
Livedo reticularis

#### Laboratory tests

Antiphospholipid antibodies: lupus anticoagulant  
anticardiolipin antibodies

#### Thrombophilia

The term 'thrombophilia' describes a predisposition to thrombosis caused by abnormally enhanced coagulation. Patients often have venous thrombosis at an early age or develop recurrent thrombotic problems.

Classical familial thrombophilia disorders are deficiencies of the naturally occurring inhibitors of coagulation protein C, protein S, and antithrombin III.

Activated protein C resistance (APCR) is a recently described thrombophilia disorder caused by an inherited mutation in the factor V gene. Heterozygosity is common (3-7% in Western European population).

Rejected patients with familial thrombophilia require lifelong anticoagulation.

Antiphospholipid antibody syndrome is an acquired disorder characterised by laboratory identification of antiphospholipid antibodies and clinical features including thrombophilia, recurrent fetal loss and thrombocytopenia.

## ANTICOAGULATION AND THROMBOLYTIC THERAPY

Two major classes of drugs are used in the management of thromboembolic disease. The *anticoagulants* heparin and warfarin are used to prevent thrombosis and limit the extension of an established clot, whilst *thrombolytic agents* such as streptokinase are used to dissolve thrombus.

### ANTICOAGULATION

#### HEPARIN

Unfractionated heparin is a naturally occurring glycosaminoglycan produced by mast cells. Low molecular weight (LMW) heparin is prepared by controlled depolymerisation of the unfractionated form. Both unfractionated and LMW heparin exert their anticoagulant properties by binding to antithrombin III (AT III) and potentiating its activity. AT III is a normal circulating anticoagulant which inhibits the actions of factor Xa and thrombin. LMW heparin differs from unfractionated heparin in having a relatively greater anti-Xa than antithrombin activity.

#### Unfractionated heparin

Standard unfractionated heparin may be used therapeutically to treat established thrombosis (usually intravenously at higher dosage) or prophylactically to prevent thrombosis (usually subcutaneously at lower dosage). Most common indications for therapeutic use are deep vein thrombosis (DVT) and pulmonary embolism (PE). A typical regimen is an intravenous loading dose of 5000 units followed by an infusion of 1000-2000 units/hour. Laboratory monitoring should start within 4-6 hours of treatment and continue daily for its duration. The objective is to keep the APTT (see p. 20) at 1.5-2.5. Should the APTT be too high it is generally adequate to stop the infusion for a short time (30-60 minutes) and restart at a reduced dose. In the event of serious bleeding requiring immediate neutralisation of heparin, the antidote protamine is given. When the APTT is too low the heparin dose should be promptly increased.

Heparin is normally continued until oral anticoagulation is therapeutic. Therapeutic doses must be prescribed with caution in patients with a bleeding tendency; examples include recent surgery, thrombocytopenia and liver dysfunction. Prophylactic heparin is most commonly given to prevent DVT and PE in patients undergoing surgery. It is particularly indicated in patients with known risk factors for venous thrombosis and in major procedures. A typical prophylactic regimen is 5000 units subcutaneously preoperatively and 5000 units 8 to 12 hourly after surgery, for 7 days or until the patient is mobile. No laboratory monitoring is necessary in routine cases - where required anti-Xa assays are used. Apart from haemorrhage, patients on heparin may develop thrombocytopenia and prolonged use can cause osteoporosis.

#### LMW Heparin

These heparins have been developed over the last decade. Compared with standard heparin they have a longer plasma half-life allowing once daily dosage. Less variation in the anticoagulant response to a fixed dose allows their use without laboratory monitoring. They may also have an improved antithrombotic to haemorrhagic ratio. At present cheaper standard heparin is often still the first choice for established thrombosis and in most prophylactic situations. However, patients at very high risk of thrombosis, for instance following major orthopaedic surgery, seem to benefit from use of LMW preparations. The convenience and probable increased safety of LMW preparations is likely to lead to their increased use in the future.

**Fig. 2 The vitamin K cycle and the action of warfarin.** The major site of warfarin action is not a direct effect on the carboxylation step needed for coagulation factor activation but on steps needed for resynthesis of active vitamin K from its epoxide form.

### WARFARIN

Oral anticoagulant drugs are derived from 4hydroxycoumarin and the standard agent is warfarin. Warfarin works by antagonising vitamin K, which is needed for the gamma carboxylation of certain glutamic acid residues which facilitate calcium binding of coagulation factors II, VII, IX and X (Fig. 2). Some indications for warfarin and desired therapeutic ranges are shown in Table 1. A reasonable starting regimen is 10 mg on each of the first 2 days and then

Table 1 Warfarin: indications and therapeutic ranges

Indication	Recommended INR
Prophylaxis of DVT including surgery in high risk cases*	2.0-2.5
Treatment of DVT and PE	2.0-3.0
Systemic embolism	
Transient ischaemic attacks	
Atrial fibrillation	
Mitral stenosis with embolism	
Recurrent DVT and PE	3.0-4.5
Mechanical prosthetic valves	
Atrial disease including myocardial infarction	

\*Heparin more commonly used.

adjustment of the dose according to the international normalised ratio (INR). A coagulation screen should always be checked before warfarin is prescribed. The maintenance dose is usually between 3 and 9 mg. Laboratory monitoring depends on the prothrombin time. Thromboplastin reagents used in this test vary and their sensitivity is labelled with an international sensitivity index (ISI) which permits reporting as an INR such that  $INR = (\text{prothrombin time})^{\text{ISI}}$ .

As it takes several days for warfarin to become therapeutic, the conventional treatment of established thrombosis is to start heparin and warfarin simultaneously and only to stop the heparin when the desired INR has been achieved. Warfarin should be used with caution in patients with a bleeding tendency. The most common side-effect is haemorrhage, the risk of serious bleeding correlating with the height of the INR. Poor control of anticoagulation and bleeding may arise from poor prescribing or compliance (i.e. over-dosage), intercurrent illness, and interaction with a potentiating drug (Table 2). A prolonged INR in a non-haemorrhagic patient may only require withdrawal of the drug for a few days. Where there is haemorrhage, warfarin can be reversed within hours by intravenous vitamin K (0.5-5 mg) and instantly by infusion of a concentrate of factors II, IX, X and VII or, alternatively, fresh frozen plasma (FFP). Guidelines are complex and significant warfarin over-dosage should be discussed with a haematologist. The duration of warfarin treatment depends on the indication. Anticoagulation may be needed for only six weeks in a patient with a limited DVT and reversible risk factors (e.g. post-surgery). Longer periods are indicated in idiopathic venous thrombosis, and lifelong warfarin treatment may be justified following recurrent episodes of venous thrombosis or where there is a known ongoing thrombotic risk such as a prosthetic heart valve, atrial fibrillation or a thrombophilic state. Community and outpatient warfarin treatment is best monitored in specialist clinics where control is audited and technologies such as computerisation exploited.

Table 2 Drugs interacting with warfarin\*

Potentiating	Antagonising
Alcohol	Oral contraceptives
Cimetidine	Spironolactone
Allopurinol	Antihistamines
Quinine	Barbiturates

Ritamycin  
Amiodarone  
Co-trimoxazole  
Metronidazole  
Tricyclics  
Aspirin and salicylates  
Anabolic steroids  
Thyroxine  
Sulphapyrazone

These are some commonly implicated agents - this is not a comprehensive list

## THROMBOLYTIC THERAPY

Until recently the role of thrombolytic agents was limited to systemic use in occasional cases of major pulmonary embolism and iliofemoral venous thrombosis, and local use in acute peripheral artery occlusion. However, it is now known that these drugs benefit patients with acute myocardial infarction, reducing infarct size, preserving ventricular function and reducing early mortality. All agents are plasminogen activators. Thus they convert plasminogen, the inactive proenzyme of the fibrinolytic system in the blood, to the proteolytic enzyme plasmin. Plasmin dissolves the fibrin of a blood clot (Fig. 3) but may also degrade normal components of the coagulation mechanism. Six agents are either in use or under investigation for patients with myocardial infarction:

- streptokinase
- urokinase
- recombinant tissue-plasminogen activator (rt-PA)
- anisoylated plasminogen
- streptokinase activator complex (APSAC)
- recombinant single chain urokinase-type plasminogen activator (rscu-PA)
- recombinant staphylokinase.

More recent drugs (e.g. rt-PA) are more specific for fibrin than earlier agents (e.g. streptokinase) but all agents are contraindicated in patients with a significant bleeding tendency.

## Anticoagulation and thrombolytic therapy

The anticoagulant drugs heparin and warfarin are used to prevent thrombosis and limit the extension of an established clot. Heparin is given intravenously or subcutaneously and acts by potentiating the activity of antithrombin III. Warfarin is given orally and acts by inhibiting vitamin K. Therapeutic treatment with both unfractionated heparin and warfarin requires careful laboratory monitoring. Thrombolytic agents are used to dissolve thrombus. They act by converting plasminogen to the proteolytic enzyme plasmin.

Fig. 3 Action of thrombolytic agents.

## THE BLOOD GROUPS

The blood group antigens exist on the surface of the red cell membrane. There are numerous blood group systems encoded by genes on different chromosomes. They are highly variable in their polymorphism and clinical significance.

The most important blood group is the ABO system. The genes encoding the ABO antigens are located on chromosome 9 and are inherited in an autosomal dominant fashion. Each antigen is a sugar residue made by a specific glycosyl transferase. The ABO system is crucial in clinical blood transfusion as there are naturally occurring IgM antibodies in the serum targeted against the non-present ABO antigens (Table 1). These antibodies necessitate the use of ABO 'compatible' blood for transfusion. For example, the administration of incompatible group A blood to a group B patient would engender a potentially fatal haemolytic transfusion reaction due to the destruction of the donor's group A red cells by the recipient's anti-A antibody.

In other blood group systems 'naturally occurring' antibodies are rare. However, 'immune antibodies', usually of IgG type, may be induced by transfusion of blood expressing different blood group antigens or maternal exposure to fetal red cell antigens. Where such immune antibodies are present, transfused blood must be matched for the relevant blood group system in addition to ABO. Maternal formation of immune antibodies against antigens of the Rhesus (Rh) blood group system, particularly the strongest antigen D, accounts for most cases of haemolytic disease of the newborn.

Table 1 The occurrence of ABO antigens and antibodies

### ABO Blood Group

#### 0ABAB

Antigens on red cells-None-A-B-A+B

Antibody in serum-Anti-A+B Anti-B Anti-A None-Frequency (%)\*-

47 42-8-3

\* In the United Kingdom Incidences vary greatly in different populations

## THE TESTING OF BLOOD

### DONOR BLOOD

The safety of blood transfusion is maximised by careful selection of donors. All donors should be in good health and, wherever possible, unpaid volunteers. Particular care is taken to exclude potential donors who may harbour infective diseases which are transmissible by blood transfusion - thus people with recent jaundice (? hepatitis), a history of recent travel to malarial areas or risk factors for HIV infection are not suitable donors.

The objective of routine testing of donated blood is to provide blood which can be selected for likely compatibility with a patient and which contains no identifiable infectious agent (See Table 2).

### TESTING BEFORE TRANSFUSION

Most incompatible transfusions are caused not by errors in the transfusion laboratory but by giving blood to the 'wrong' patient (i.e. not the patient whose serum was tested prior to the transfusion). The source of such mistakes is usually inaccurate documentation on forms and specimens or inadequate procedures for identifying patients prior to transfusion.

If tests on donor and recipient blood confirm matching for ABO and Rhesus groups, the transfusion will be compatible in around 98% of cases. The sequence of tests prior to transfusion thus also includes antibody screening of the patient's serum and crossmatching to ensure compatibility in the remaining 2%.

**Most incompatible blood transfusion arise from clerical errors and mistaken patient identity.**

### Blood grouping

The recipient's red cells are tested for ABO and Rhesus antigens and the serum tested for naturally occurring antibodies to confirm the ABO group. Blood grouping tests traditionally rely on the visual identification of agglutination of red cells induced by the presence of antibodies against antigens present on the cell surface (Fig. 1). Newer technologies include the use of gels (Fig. 2).

Table 2 Routine testing of donated blood

ABO group

Rhesus group (at least D)

Red cell antibody screen

Hepatitis B surface antigen

Antibody to hepatitis C

Antibody to H IV- 1

Antibody to treponema pallidum (syphilis)

Antibody to HTLV-1 (in USA)

Fig. 1 ABO blood grouping on a microplate.

Fig. 2 Blood grouping using a gel system. (a) ABO and RhD grouping. (b) Rh and Kell grouping.

### Antibody screening

The patient's serum is tested against three standard sets of screening red cells of known antigenic type. This is to detect immune or 'atypical' antibodies (i.e. non-ABO) which might destroy donor red cells. Clinically relevant antibodies are generally reactive at 37°C. If an antibody is found, then blood which is negative for the relevant antigen must be selected. A number of different techniques are used for antibody identification - agglutination may be enhanced by enzyme treatment of red cells, use of low ionic strength saline (LISS) or the antiglobulin (Coombs') test (Fig. 3).

### Crossmatching

The final compatibility check is to mix the patient's serum with red cells from each donor unit. The aim is to highlight any earlier errors in grouping or antibody screening and to identify the presence of antibodies against rare antigens not present on the screening cells. Usually a simple one tube technique with the addition of antihuman globulin reagent is used. The minor crossmatch - mixing of donor serum with patient red cells is not routinely performed.

### PRACTICALITIES OF BLOOD ORDERING

Where blood transfusion is definitely required and adequate time is available, tests proceed as above and compatible units are issued. In emergencies, blood is sometimes needed more quickly than this routine testing allows. Normal procedures may be adapted to speed up issue of group specific blood. Only rarely is it necessary to give group 0 Rhesus negative blood.

The bulk of blood is crossmatched for use in elective surgical procedures. Where there is only a small chance (less than 10%) that transfusion will be required it is reasonable to limit wastage by adopting a 'group and save' policy. The patient's blood group is determined and the serum screened for atypical antibodies. Provided the screen is negative, blood is not routinely crossmatched. Most hospitals have implemented a formal surgical blood order schedule with guidelines for common operations (Table 3). Such guidelines are generalisations and special provision is made for unusually difficult procedures or patients who are judged to be at a higher than average risk of haemorrhage.

### Blood groups and blood testing

The blood group antigens exist on the surface of the red cell membrane. Blood groups are highly variable in their polymorphism and clinical significance.

The ABO system is crucial in blood transfusion as there are naturally occurring IgM antibodies in the serum targeted against non-present ABO antigens - this necessitates the use of ABO 'compatible' blood. Blood donors are carefully selected and donor blood tested to exclude transmissible infections.

Testing of donor and recipient blood for ABO and Rhesus groups, antibody screening of the recipients serum, and crossmatching are routinely performed before transfusion to ensure compatibility.

Most incompatible blood transfusions arise from clerical errors and mistaken patient identity.

**Table 3 Possible guidelines for blood ordering in a few common operations.** Protocols vary between hospitals and should be based on previous blood usage.

Procedure	Recommendation*
Cholecystectomy	Group and save
Colectomy/hemicolectomy	2
Breast biopsy	Group and save
Heart valve replacement	8
Resection abdominal aortic aneurysm	8
Abdominal hysterectomy	Group and save
Total hip replacement	3
Transurethral resection of prostate	Group and save

Figures refer to the number of units of red cells crossmatched prior to surgery.

## RED CELL TRANSFUSION

Two questions need to be answered before transfusion of red cells is undertaken:

1. Is it indicated?
2. If it is indicated, which red cell preparation should be used?

Some general indications for red cell transfusion are listed in Table 1.

Whole blood is now rarely available for the treatment of acute blood loss. Haemorrhage requires transfusion of fluids, including plasma expanders, to maintain blood volume and red cell concentrates to raise haemoglobin. For correction of anaemia, red cell concentrate or concentrate in 'optimal additive solution' are used. It is important to appreciate that many patients with anaemia do not require transfusion, just prescription of the appropriate haematinic (e.g. iron deficiency).

### Practicalities of red cell transfusion

All doctors and nurses involved in the prescription and administration of blood should follow local guidelines with respect to patient identification and the checking of the compatibility and viability of the transfused units. Critical information is contained on the blood bag and the attached compatibility label. No discrepancies are permissible.

In shocked patients blood is transfused rapidly, the precise rate dependent on the monitoring of vital signs such as pulse, blood pressure and urine output. Transfusion for correction of anaemia is usually a more elective process. Units of red cell concentrate are typically given over 24 hours and a rise of around 10g/l of haemoglobin can be expected from each unit. Red cells are infused via specially designed sterile 'giving sets' which contain 170 µm filters. Cannulation for blood transfusion is discussed on page 99. Careful monitoring is particularly important during the first 10 minutes of each unit - subsequently the pulse and blood pressure are checked at least every 30 minutes.

### Complications of red cell transfusion

#### Immediate

**Haemolytic transfusion reactions.** These potentially fatal reactions arise from the transfusion of incompatible blood (usually for ABO). Symptoms often occur within minutes and may include chest, abdominal and loin pain, vomiting, a 'burning' skin, dyspnoea and headache. Common signs are fever, tachycardia and hypotension. Renal failure and disseminated intravascular coagulation (DIC) can follow. Once a haemolytic reaction is suspected, the transfusion should be stopped and the venous access used to give crystalloid. The transfused unit should be checked (is another patient about to get a 'wrong' unit due to a mix up?) and the blood bank informed. Initial investigations must include blood samples from the patient for a blood count and film, blood group, antibody screen and direct antiglobulin test. The blood bank will also repeat tests on the donated unit. Management of complications will require senior advice and often intensive care. The overall mortality of ABO incompatible transfusion is approximately 10%. Some are fortunate and have trivial or even a complete lack of symptoms.

**Table 1 Major indications for red cell transfusion**

#### To replace blood loss

Trauma  
Surgery  
Other haemorrhage (e.g. gastrointestinal bleed)

#### To correct anaemia

Marrow failure (e.g. aplastic anaemia, leukaemia) Haemoglobinopathies (e.g. thalassaemia, sickle cell disease)  
Chronic disorders (e.g. renal failure, malignancy) Severe haemolysis (e.g. haemolytic disease of the newborn)  
The final decision to transfuse requires consideration of the patients age, clinical state, and haemoglobin concentration.

#### Non-haemolytic transfusion reactions.

# CE measures treats

Volts and Oscillations (EMG, EEG)

Amps and Oscillations (ECG)

Resistance (GSR)

Hydration

Oxidation (Redox potential)

Ph acid vs alkalinity

Reactivity evoked potential to voltammetric fields of substances (TVEP) over 228,000 measures a second of these energetic factors

Brain wave and emotions with (MCES)

Pain with (MENS) (TENS)

Trauma or wounds (EWH)

Electro Weakness Ph, Redox disorder (VARHOPE Correction)

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The majority of adverse reactions to blood are 'febrile reactions' caused by antileucocyte antibodies in the patient. Uncomplicated febrile reactions are simply managed by slowing the transfusion and giving aspirin. If further transfusions are needed, leucocyte depleted blood can be obtained. Occasionally patients develop allergic reactions with urticaria, wheezing and (rarely) anaphylaxis.

**Local thrombophlebitis** may occur at the cannulation site.

**Circulator overload.** Care must be taken not to transfuse too rapidly, especially in elderly patients with heart disease.

#### Delayed

**Infection.** Bacteria, viruses and parasites may all be transmitted via blood transfusion. As already discussed in the previous section, blood is screened for the relevant agents to minimise this risk. It is now known that the great majority of cases of transfusion associated hepatitis previously described as 'Non-A, Non-B' are attributable to the hepatitis C virus. The significance of transmission of infection from blood can depend on the status of the recipient. Thus, cytoinegalovirus (CMV) is of little relevance in healthy adults but potentially life-threatening in a patient receiving a bone marrow transplant or in a low birth-weight premature infant.

Fig. 1 Unit of red cells.

**Delayed transfusion reactions.** These occur approximately 5-10 days after transfusion and are caused by a previously undetected antibody being boosted by transfusion of incompatible cells. Characteristic features include fever, jaundice and a failing haemoglobin. They are only rarely fatal.

**Iron overload.** A unit of blood contains around 250 mg of iron. Iron is only lost from the body in small amounts and repeated transfusion can lead to accumulation and toxic effects identical to those seen in haemochromatosis. Where repeated transfusion is predictable in a younger person (e.g. in thalassaemia), chelation of iron with parenteral desferrioxamine limits overload and prolongs life.

Table 2 Major red cell preparations

Preparation	Approximate packed cell volume	Approximate volume of pack (mls)
Whole blood	0.4	
Red cell concentrate (plasma reduced)	0.6	
Red cell concentrate in optimal additive solution (SAG-M)	0.6	

#### Massive blood transfusion

Massive transfusion is defined as replacement of the patient's whole blood volume by stored allogeneic blood in less than 24 hours. Patients receiving such large transfusions are usually already critically ill, but further problems can arise due to the inevitable deficiencies of stored blood. Shortage of clotting factors and platelets in transfused blood may exacerbate haemorrhage. It is important to monitor haemostasis by checking the basic coagulation screen (page 20) and replacing components accordingly. Metabolic disturbances are less common but include hyperkalaemia, hypocalcaemia, acidosis and citrate toxicity. Rapid transfusion can cause hypothermia; this can be minimised by carefully controlled blood warming.

#### Autologous blood transfusion

Use of the patient's own blood for transfusion rather than allogeneic blood minimises the risk of infection. The most common method is to arrange for patients to 'predeposit' up to four units of blood in the weeks prior to elective surgery. It has been calculated that up to 10% of all transfusions could be provided in this way. An alternative approach is the use of specially designed equipment to salvage blood lost during surgery and reinfuse it back into the patient.

## TRANSFUSION OF PLATELETS AND GRANULOCYTES

### Platelet transfusion

This is used to treat or prevent haemorrhage in patients with significant thrombocytopenia. It is more useful where platelets are low due to underproduction (i.e. marrow failure) or dilution than where thrombocytopenia is due to immune destruction as in ITR. Platelets are collected either from routine blood donations or from a single donor by plasmapharesis. They should ideally be matched with the patient for ABO and Rhesus. The standard dose for an adult is either a single plasmapharesis donation or 46 pooled standard donations. Where repeated platelet transfusions are given, patients can become sensitised against class I HLA antigens (HLA-A, B and C) absorbed onto the platelet surface with the result that they derive a lower increment in platelet count than would be predicted ('platelet refractoriness'). In these cases, platelet donors matched with the recipient's HLA class I type can be selected. Platelet transfusion can cause non-haemolytic reactions and can transmit infection as for red cells.

Table 3 Possible indications for use of fresh frozen plasma

Disseminated intravascular coagulation (DIC)  
Severe liver disease (e.g. prior to liver biopsy)  
Coagulopathy of massive blood transfusion  
Reversal of oral anticoagulation where significant bleeding'  
Replacement therapy of some rare congenital factor deficiencies  
Bleeding in haemorrhagic disease of newborn/malabsorption vitamin K  
Thrombotic thrombocytopenic purpura (with plasma exchange)  
Depletion of coagulation factors following thrombolysis

Prothrombin complex and factor VII concentrate probably better where available.

### Granulocyte (neutrophil) transfusion

Neutrophils for transfusion are collected by plasmapharesis of healthy donors who preferably should be cytomegalovirus (CMV) seronegative. Granulocytes transfusion is infrequently used and the indications uncertain, particularly now that the neutrophil count may be increased with growth factors such as GCSF. However, granulocytes may be helpful in a patient with severe neutropenia and a focus of infection not responsive to treatment with antibiotics and growth factors.

## TRANSFUSION OF PLASMA AND PLASMA PRODUCTS

A wide range of plasma products is available for therapeutic use:

**Fresh frozen plasma (FFP).** Plasma is collected from whole blood or derived from plasmapharesis prior to rapid freezing. FFP contains the full range of coagulation factors and indications for use are shown in Table 3. The normal dose in an adult is one litre. FFP can transmit infection and cause immunological reactions - it is not suitable for volume expansion alone.

**Cryoprecipitate.** This is prepared from FFP by slow thawing and separation of the resultant precipitate. It is rich in fibrinogen and may be useful in the treatment of DIC and management of massive blood transfusion. In haemophilia and von Willebrand's disease it has been superseded by factor concentrates.

**Factor VIII and IX concentrate.** Use of these is discussed.

**Albumin.** This is produced by fractionation of pooled plasma. Solutions for clinical use include human albumin 4.5/5 %, human albumin 20% and plasma protein fraction (PPF). Major clinical indications are in resuscitation (often combined with crystalloid), replacement of plasma protein in severe burns and symptoms arising from hypoproteinaemia.

**Immunoglobulins.** These can be specific and used in passive prophylaxis against a range of infections (e.g. varicella-zoster, tetanus) or to prevent haemolytic disease of the newborn (anti-Rhesus D). 'Non-specific' immunoglobulins are used for passive prophylaxis against hepatitis A, treatment of congenital or acquired hypogammaglobulinaemia and in selected autoimmune disorders (e.g. ITP).

### Blood transfusion - clinical practice

Before red cell transfusion is undertaken the indication should be confirmed and the optimal red cell preparation selected.

Red cell transfusion can cause both immediate complications (e.g. haemolytic transfusion reaction) and delayed complications (e.g. infection, iron overload).

Platelet transfusion may be helpful in the management of thrombocytopenia. Granulocyte transfusion is occasionally indicated in neutropenia.

A wide range of plasma products is available for transfusion. Selection of the appropriate product requires an understanding of the therapeutic benefit and possible side effects.



## THE IMMUNOSUPPRESSED PATIENT

Many patients with blood disorders are immunosuppressed. Patients with aggressive haematological malignancies such as leukaemia and high grade non-Hodgkin's lymphoma have their immune function initially compromised by the disease and then further depressed by chemotherapy. Others have more subtle deficiencies; patients with low-grade non-Hodgkin's lymphoma and with 'benign' diseases such as idiopathic thrombocytopenic purpura (ITP) and hereditary spherocytosis who have had splenectomy performed are also at increased risk of infection.

**Fig. 1** Aspergillosis complicating prolonged neutropenia

An increased susceptibility to infection can arise from multiple factors (Table 1). Neutropenia and neutrophil dysfunction are probably the most important causes of infectious complications in patients with leukaemia. Unlike many other forms of immunosuppression, neutropenia is easy to quantify - the risk of infection rises appreciably at counts below  $0.5 \times 10^9/l$  and is greatest where the count is below 0.1. Lymphopenia and lymphocyte dysfunction are seen in lymphoid malignancy and after chemo- and radiotherapy. Defects in humoral immunity are particularly seen in patients with chronic lymphoid malignancies and in myeloma. The likelihood of infection is related to the severity of hypogammaglobulinaemia.

Other common immunosuppressive factors are the loss of mucosal or skin integrity due to damage from disease or treatment, and the presence of indwelling venous catheters.



## TYPES OF INFECTION

### Bacteria

Bacterial infections in neutropenic patients are usually caused by the spread of commensal flora to previously sterile sites. Fatal septicaemia can result from bowel-associated gram-negative bacilli such as *Pseudomonas aeruginosa*, *E. Coli*, *Klebsiella* spp. and *Proteus* spp. Gram-positive cocci are becoming increasingly common causes of nosocomially acquired infections. The skin pathogen *Staphylococcus epidermidis* often colonises indwelling venous catheters. The use of broad-spectrum antibiotics can lead to the emergence of toxin-producing *Clostridium difficile* in the stools. Bacterial infection in neutropenic patients may be overt - for instance a chest infection with a productive cough or the presence of infected skin lesions (Fig. 1). However, bacterial sepsis can equally present with non-specific malaise and a pyrexia. In the latter case extensive cultures including blood, nose, throat, stool and urine are indicated.

**Fig. 2** Herpes zoster following an allogeneic bone marrow transplantation

### Table 1 Possible factors predisposing to infection in haematology patients

#### Cellular defects

Neutropenia and neutrophil dysfunction

Lymphopenia and lymphocyte dysfunction

#### Humoral defects

Reduced antibody production

#### Anatomic defects

Reduced mucosal barriers (e.g. mucositis)  
Indwelling venous catheters

#### Splenectomy

#### Fungi

The incidence of invasive fungal infections is increasing and they are a major cause of morbidity and mortality in patients with haematological malignancy.

The most widespread fungal pathogen is *Candida*. Oral and colonic carriage of the organism is common in healthy people. Oropharyngeal candidiasis frequently complicates neutropenia and becomes invasive in 25% of cases. Disseminated candidiasis usually presents with a persistent fever and no diagnostic clinical features. Possible organ involvement includes the kidney, lung, heart and liver. Cutaneous emboli may lead to a nodular skin eruption whilst exudative retinal lesions can be seen through the ophthalmoscope. Unfortunately, *Candida* spp. are grown from blood cultures in only 20% of patients with definite candidiasis. A number of tests are available to detect circulating antigen but all have limited sensitivity.

The second most common fungal species in immunosuppressed patients is *Aspergillus*. Infection is usually via the inhalation of airborne spores and is mainly pulmonary. A chest X-ray may show pneumonia and cavitation (Fig. 2). Other infected sites can include the paranasal sinuses, skin, central nervous system and eye. Even in disseminated disease, blood and sputum cultures are rarely positive. Open lung biopsy gives the best diagnostic yield from cultures with bronchoscopy (biopsy or lavage) a better tolerated alternative in ill patients. *Aspergillus* is present in up to 20% of neutropenic patients at autopsy.

#### Viruses

Most viral infection in immunosuppressed patients is caused by reactivation of latent organisms. Patients with deficient cell mediated immunity (e.g. acute lymphoblastic leukaemia (ALL), bone marrow transplantation, chronic lymphatic leukaemia) are particularly susceptible. Important pathogens include herpes simplex, varicella-zoster and cytomegalovirus (CMV). Clinical manifestations range from relatively trivial mouth ulcers attributable to herpes simplex through herpes zoster (shingles) (Fig. 3) with the risk of dissemination to the potentially fatal CMV pneumonitis which complicates allogeneic bone marrow transplantation. Measles can be a fatal illness in children with ALL. There may be no specific diagnostic features of viral infection and it must be considered as a possible cause of a febrile illness in the immunosuppressed patient. Newer methods for detecting viruses include molecular probes for viral DNA and monoclonal antibodies specific for viral antigens. These technologies are already proving useful in diagnosing CMV infection after marrow transplantation.

#### Pneumocystis carinii

*Pneumocystis* causes a potentially fatal bilateral pneumonia in patients with depressed cell mediated immunity. In haematological practice it mostly affects patients receiving intensive chemotherapy regimens or bone marrow transplantation, and haemophiliacs infected with the HIV virus.

### PREVENTION OF INFECTION IN THE IMMUNOSUPPRESSED PATIENT

#### Neutropenia

General measures include the isolation of the patient, laminar airflow rooms, strict hygiene and avoidance of possible contaminants (e.g. uncooked food). Simple measures such as hand washing by staff are crucial in reducing infection rates.

As many bacterial infections are attributable to endogenous bowel associated organisms, antibiotics have been used to 'decontaminate' the gut during periods of neutropenia. A more recent approach is that of selective decontamination of the aerobic bowel flora. The combination of cotrimoxazole and colistin reduces the incidence of infections. An increasingly popular alternative is the quinolone antibiotic ciprofloxacin.

Antifungal prophylaxis is available in the form of ketoconazole, itraconazole and fluconazole. Ketoconazole can cause serious liver damage and the choice is between the other agents. Fluconazole has superior bioavailability and offers effective protection against *Candida* but is less effective against a *Aspergillus* than itraconazole. Viral infections are frequently seen in the context of neutropenia and the antiviral drug acyclovir is accordingly often added to prophylactic regimens.

#### Depressed cell mediated immunity and hypogammaglobulinaemia

Impaired cell mediated immunity leads to an increased risk of *Pneumocystis carinii* pneumonia and viral infections. Standard prophylaxis against *Pneumocystis* is oral cotrimoxazole three times weekly. Nebulised pentamidine may be substituted where cotrimoxazole is not tolerated. Acyclovir is effective in reducing the incidence of viral infections. The more toxic drug gancyclovir can be used after marrow transplantation to give additional protection against CMV. Patients with low-grade lymphoproliferative disorders and myeloma can have significant hypogammaglobulinaemia and suffer recurrent infection. Regular infusions of immunoglobulin are often helpful in these cases.

#### Post-splenectomy

### TREATMENT OF INFECTION

#### The pyrexial neutropenic patient

A common clinical problem in haematology is the management of the patient with neutropenia (less than  $1 \times 10^9/l$  neutrophils) who develops a pyrexia (a single temperature above 39°C or two successive measurements above 38°C). Such patients can rapidly succumb to bacterial infection and need prompt empirical treatment with broad spectrum intravenous antibiotics even before the infectious pathogen is identified. Blood and other cultures are taken prior to starting antibiotics and a chest X-ray is helpful: investigations, however, should not substantially delay treatment. A microbiological diagnosis is made in only half of these cases.

The empirical antibiotic regimens are designed to provide protection against commonly implicated organisms, particularly those causing life-threatening infection (e.g. *Pseudomonas*). Regimens are constantly changing - the major groups of drugs are summarised in Table 2. Most clinicians rely on a combination of antibiotics. Monotherapy with ceftazidime or ciprofloxacin may be adequate to prevent death from gram-negative infection, but the high incidence of grampositive infections make the addition of a glycopeptide (e.g. teicoplanin) advisable. Persistent pyrexia or clinical deterioration on first line antibiotics is a difficult management problem. Often the infectious agent is unknown. The usual approach is to continue investigations whilst making a change in the antibiotic regimen. A lack of response necessitates the introduction of amphotericin B as empirical antifungal treatment. Growth factors (e.g. GCSF) may be given to shorten the period of neutropenia and granulocyte transfusions are worth consideration in well documented bacterial infections unresponsive to antibiotics.

**Treatment of specific infections** Intravenous amphotericin B is indicated for proven systemic aspergillosis as well as in the empirical role outlined above. Oropharyngeal candidiasis can often be treated with local agents (e.g. nystatin) with the addition of oral fluconazole in resistant cases. Amphotericin B is effective against systemic candidiasis with intravenous fluconazole a possible alternative. Herpes simplex and varicella zoster infections are best treated with acyclovir. Gancyclovir is used for CMV infection after marrow transplantation. *Pneumocystis carinii* pneumonia is equally effectively treated by either high dose cotrimoxazole or pentamidine.

Table 2 Groups of antibiotics used in the empirical treatment of infection in neutropenia

Group	Examples
Antipseudomonal penicillins	Aztreonam, piperacillin
Aminoglycosides	Gentamycin, amikacin
Cephalosporins	Ceftazidime
Quinolones	Ciprofloxacin
Carbapenems	Imipenem
Glycopeptides	Teicoplanin, vancomycin

Note: some agents have been used alone (e.g. ceftazidime) but combinations are more commonly used (e.g. penicillin + aminoglycoside, cephalosporin + glycopeptide).

#### The immunosuppressed patient

Many patients with blood disorders are immunosuppressed. Possible factors predisposing to infection include neutropenia, lymphopenia, reduced antibody levels and anatomical defects.

Bacteria, fungi and viruses can all cause severe systemic infection in an immunosuppressed patient.

Measures to prevent infection in the immunosuppressed patient include isolation of the patient, strict hygiene and prophylactic use of antimicrobial agents.

Infection in a neutropenic patient generally requires empirical treatment with broad-spectrum antibiotics. Persisting fever or clinical deterioration necessitates a change in antibiotics and/or empirical antifungal treatment.

## HAEMATOLOGICAL CHANGES

Several haematological changes occur in normal pregnancy (Fig. 1). Beginning in the sixth week there is an increase in plasma volume accompanied by an increase in red cell mass. The plasma volume expansion peaks at around 24 weeks when it is approximately 40% greater than in a non-pregnant woman. As the increase in red cell mass is more modest (15-25%) *a dilutional anaemia* is inevitable. In practice the haematocrit and haemoglobin level start to fall at 6-8 weeks and reach a trough at around 20 weeks. It is unusual for the haemoglobin level to fall below 100g/l and if this happens another cause for anaemia should be sought. Negative iron balance can be regarded as routine in pregnancy and as discussed below frank iron deficiency commonly occurs.

The other major changes which may be regarded as a physiological consequence of pregnancy affect the coagulation system. There are increases in the levels of the coagulation factors VII, VIII and X and a marked increase in plasma fibrinogen. The resulting hypercoagulability is helpful in limiting the likelihood of life-threatening bleeding at delivery but it does lead to an increased risk of thromboembolism. Surprisingly, there is conflicting evidence regarding platelet count, size and function in pregnancy. There may be a small fall in platelet number and an increase in mean platelet volume (MPV) in the last few weeks.

### ANAEMIA IN PREGNANCY

There are several causes of anaemia in pregnancy. The most common scenario is an exacerbation of the usual dilutional anaemia by deficiency of iron and/or folate.

The identification of iron deficiency relies upon normal laboratory tests. However, even in women with no overt clinical deficiency there is a progressive fall in serum iron and increase in total iron binding capacity (TIBC) through pregnancy. Routine dietary supplementation with modest amounts of iron (e.g. ferrous sulphate 200 mg daily) leads to a significant increase in haemoglobin level at term compared with women receiving no supplements. The other major type of anaemia in pregnancy is megaloblastic anaemia. This usually results from deficiency of folate. As for iron, folate requirements are increased during pregnancy and the diet is frequently inadequate to meet this demand. Megaloblastic anaemia most often presents as a macrocytic anaemia in the third trimester or postpartum. It is normal practice to give folate supplements in pregnancy. The amount of folate administered orally should be large enough to routinely avoid megaloblastic anaemia but not so large as to risk masking pernicious anaemia with vitamin B<sub>12</sub> deficiency which does occasionally occur in pregnancy. The usual dose is 200-500 mcg daily. Folate deficiency in pregnancy has been linked with an increased incidence of neural tube defects in the fetus and recent recommendations for planned pregnancies are the use of folate supplements (400 mcg daily) prior to conception and then particularly in the first twelve weeks. Higher doses of folate are recommended to prevent recurrence of neural tube defects. There is no justification for the prescription of multi-ingredient vitamin preparations in pregnancy but a combined iron and folate tablet of adequate dosage may be prescribed.

It should be remembered that not all anaemia in pregnancy is caused by deficiency states. Other blood disorders may present in pregnancy and chronic blood diseases such as sickle cell anaemia can be especially difficult to manage at this time.

Fig. 1 Common haematological changes in normal pregnancy.

### THROMBOCYTOPENIA IN PREGNANCY

With the introduction of automated cell counters which routinely provide a platelet count, the incidence of thrombocytopenia in pregnancy has increased and it is now a common clinical problem.

Some women have an obvious systemic disorder such as pre-eclampsia; disseminated intravascular coagulation (DIC) in pregnancy is further discussed below. However, the majority of women are symptomatically well with an

apparently normal pregnancy. In these cases thrombocytopenia can be divided into two categories, with differing clinical implications for the mother and fetus.

#### Incidental thrombocytopenia

Incidental thrombocytopenia of pregnancy accounts for about three-quarters of all cases. Thrombocytopenia is mild to moderate ( $70-150 \times 10^9/l$ ) and the woman is otherwise well. There is no past history suggesting a cause for the low platelet count and particularly no history of idiopathic thrombocytopenic purpura (ITP). The overwhelming majority of these mothers can have normal antenatal observations and a normal delivery. The incidence of thrombocytopenia in their babies is not greater than in the general population. Diagnosis of incidental thrombocytopenia is made by exclusion as there is no specific diagnostic test.

#### ITP in pregnancy

The management of pregnancy in a woman with known chronic ITP is problematic as severe thrombocytopenia may be a threat to the mother and there is also a risk of the child becoming thrombocytopenic. The latter complication arises as the causative IgG anti-platelet autoantibody in the mother freely crosses the placenta and can target fetal platelets. Fortunately, the majority of babies escape - thrombocytopenia is seen in approximately 5-10% of neonates and is severe (less than  $20 \times 10^9/l$ ) in only half of these cases. *All management decisions* must acknowledge that fetal thrombocytopenia is uncommon and fetal morbidity rare. In this context, aggressive treatment of all mothers with ITP with corticosteroids and/or intravenous immunoglobulin and routine delivery by caesarian section are probably not justified. Attempts have been made to try and predict the likelihood of thrombocytopenia in the neonate by measuring fetal scalp blood platelet counts and platelet antibodies but success has been limited. A conservative approach with normal delivery and an immediate neonatal platelet count is gaining support. If the baby's count is low or failing, intravenous immunoglobulin can be given. Because of its low incidence of side effects, intravenous immunoglobulin is probably the treatment of choice for severe maternal thrombocytopenia.

### COAGULATION ABNORMALITIES IN PREGNANCY

#### Thromboembolism and anticoagulant therapy

Pulmonary embolism (PE) remains a major cause of maternal death. Approximately half of fatal PEs occur antepartum and half postpartum, the majority of the latter in the first two weeks of the puerperium. The precise incidence of deep vein thrombosis (DVT) and non-fatal PE in pregnancy is not known as there is a lack of reliable data. Once a DVT has occurred the risk of recurrence is around 15%. Other factors increasing the risk of thrombosis in pregnancy include caesarian section, obesity, incidental surgical procedures, a history of thrombotic problems or familial thrombophilia, and systemic disorders where there is significant blood loss or dehydration. Both the anticoagulants commonly used in clinical practice, heparin and warfarin, require special consideration in pregnancy.

**Heparin.** Neither unfractionated standard heparin or low molecular weight heparin cross the placenta and there is no evidence of a risk of fetal haemorrhage or any teratogenic effect. However, prolonged heparin therapy may lead to maternal osteopenia and the drug can also be associated with thrombocytopenia and allergic reactions.

**Warfarin.** Warfarin is not significantly secreted in breast milk and treatment is safe during lactation. However, it readily crosses the placenta and is a known teratogen producing a specific warfarin embryopathy at around 69 weeks (approximately 5% incidence). Thus, heparin should be substituted for warfarin in the first trimester. There may be a risk of fetal haemorrhage secondary to warfarin throughout pregnancy, particularly if anticoagulant control is poor, and the risk to mother and fetus becomes unacceptable in the antepartum period. It should therefore be discontinued at 36 weeks and heparin substituted until after delivery wherever possible.

#### DIC in pregnancy

DIC is associated with a wide variety of situations in pregnancy (Fig. 2). The chief characteristics and pathogenesis of DIC are discussed. In pregnancy, DIC may manifest as a chronic compensated state or as life-threatening haemorrhage. The latter is a frightening medical emergency and there should be a planned regime of management with input from an obstetrician, haematologist, physician, anaesthetist and nurse (Table 1). It is imperative that the source of bleeding is identified and addressed as soon as possible. It is often shock which triggers DIC with a resultant increase in bleeding.

#### HELLP syndrome

HELLP is an acronym for microangiopathic haemolysis (H), elevated liver enzymes (EL) and low platelets (LP). The syndrome complicates severe preeclampsia, and there are the laboratory abnormalities of DIC. The mainstay of treatment is delivery of the fetus.

#### Table 1 General guidelines for the management of acute obstetric haemorrhage

Secure venous access and consider insertion of central line to measure central venous pressure (CVP)  
Seek additional (preferably senior) medical help  
Collect samples for urgent blood count, crossmatching and coagulation screen; liaise with haematology laboratory  
Restore blood volume - may have to use unmatched blood of patient's ABO and Rh group (preferred to group 0 Rh negative)  
Address source of bleeding  
Blood product replacement as necessary

#### PREGNANCY

Normal pregnancy is accompanied by a modest dilutional anaemia. Deficiency of iron and/or folate frequently exacerbates the normal dilutional anaemia. Thrombocytopenia is most often 'incidental' and of little significance. Idiopathic thrombocytopenic purpura (ITP) may require treatment but a normal delivery is usual and severe neonatal thrombocytopenia is rare. There is a hypercoagulable state in pregnancy and pulmonary embolism remains a major cause of maternal death. Disseminated intravascular coagulation (DIC) can complicate pregnancy and cause life-threatening haemorrhage.

## PEDIATRIC HAEMATOLOGY

Many of the blood disorders encountered in children have been discussed in the preceding pages. For instance, acute lymphoblastic leukaemia is the most common leukaemia of childhood, haemophilia is usually diagnosed in infancy and the haemoglobinopathies are a significant cause of ill health in children worldwide. Chronic and severe diseases of the blood pose particular problems in childhood and usually are best managed by a paediatrician with a special interest in haematology or in a combined paediatric/haematology clinic. The child's growth and development, and educational needs often require special attention. In this section we discuss some haematological disorders encountered in paediatric practice which are not addressed elsewhere.

### NORMAL VALUES

It is important to appreciate that the normal ranges for many haematological tests vary with age. Table I illustrates reference values for the total white cell count (WCC) and the differential count in children. More detailed listings of normal ranges of laboratory tests in childhood can be found in specialized paediatric haematology texts.

Table 1 Normal white cell counts in children ( $\times 10^9/l$ )

Age	White Cell Count	Neutrophils	Lymphocytes
Birth (full term)	18 ± 8	5-13	3-10
Day 3	15 ± 8	3-5	2-8
1 month	12 ± 7	3-9	3-16
2-6 months	12 ± 6	1.5-9	4-10
2-6 years	10 ± 5	1.5-8	6-9
6-12 years	9 ± 4	2-8	1-5

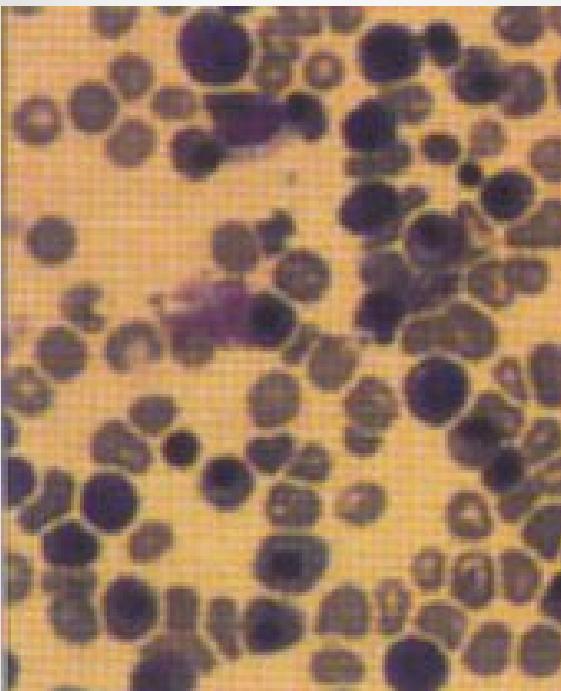
### NEONATAL DISORDERS

#### Haemolytic disease of the newborn

Haemolytic disease of the newborn (HDN) is a disease of the fetus and newborn child. The haemolysis is caused by maternal IgG antibodies traversing the placenta and attaching to fetal red cells which are destroyed in the child's reticuloendothelial system. The antibodies are directed against a fetal red cell antigen not shared by the mother. Incompatibility for one of a large number of different red cell blood group systems can cause HDN but most cases of clinically significant disease affect a Rhesus (Rh)D-positive child where the mother is RhD negative. Sensitisation of the mother (i.e. the formation of anti-D) occurs following the haemorrhage of fetal red cells into the maternal circulation. This usually occurs at parturition following a normal pregnancy but may also arise earlier in pregnancy or following abortion. ABO incompatibility between mother and fetus gives some protection against sensitisation to RhD as fetal red cells are quickly destroyed by the mother's naturally occurring anti-A or anti-B antibodies. Unfortunately, in most cases baby and mother are ABO compatible. With the considerable success of prophylaxis against HDN due to RhD incompatibility (see below) the most common cause of the disorder is the formation of immune antibodies against ABO; most cases are associated with only mild haemolysis.

#### Diagnosis

Severe HDN can result in intrauterine death. In the newborn child the presentation is entirely dependent on the degree of haemolysis but common features include anaemia, jaundice, oedema and hepatosplenomegaly. High levels of circulating unconjugated bilirubin may lead to high frequency deafness or deposition in the basal ganglia with spasticity and other neurological symptoms and signs ('kernicterus'). Further investigation of the anaemia



reveals features typical of haemolysis (Fig. 1) with a positive direct antiglobulin test (DAT). In HDN due to RhD incompatibility the baby is RhD positive and the mother RhD negative with a high level of anti-D.

#### Management

Management of HDN is complex, requiring close liaison between the haematology laboratory and obstetrician. The severity of disease in the fetus may initially be gauged by serial measurements of maternal anti-D; where there is a possibility of severe disease amniocentesis with spectroscopic measurement of bile pigment in amniotic fluid allows assessment of the degree of haemolysis. Intrauterine transfusion or premature delivery are indicated for life-threatening disease. At birth exchange transfusion is considered for neonates with significant anaemia and/or high bilirubin levels. Phototherapy may be used in the

management of kernicterus.

Fig. 1 Peripheral blood film in a newborn child with severe HDN. Note the numerous nucleated red cells and polychromasia.

#### RhD prophylaxis in RhD-negative mothers

The breakthrough in the prevention of HDN has been the introduction of Rh prophylaxis (Fig. 2). A dose of Rh anti-D immunoglobulin (Ig) is given to all Rh-negative mothers who deliver an Rh-positive infant. A larger than average fetomaternal haemorrhage necessitates a greater dose of anti-D Ig. It is possible that anti-D administration prevents HDN by simply removing the fetal D-positive cells, or another immunological mechanism may be operating. General recommendations for Rh prophylaxis are shown in Table 2. As some women undoubtedly become sensitised earlier in a normal pregnancy routine antenatal prophylaxis has been recommended; however, this is not currently universally performed.

Table 2 Recommendations for Rh prophylaxis

#### Rh prophylaxis after delivery

Anti-D (usually 500 iu) is given within 72 hours in Rh-negative mothers where the infant is Rh-D positive (or group undetermined). If there is a large fetomaternal haemorrhage (assessed in a Kleihauer test) additional anti-D is given

#### Rh prophylaxis and abortions

In Rh-D negative mothers anti-D is given after all therapeutic abortions and after spontaneous threatened abortions later than 12-13 weeks gestation (usual dose 250 iu before 20 weeks and 500 iu after 20 weeks)

#### Rh prophylaxis during pregnancy

Anti-D is given after possible sensitising events in Rh-negative women. These include: amniocentesis chorionic villous sampling, abdominal trauma, external cephalic version, antepartum haemorrhage, ectopic pregnancy (usual dose of anti-D is 250 iu before 20 weeks and 500 iu after 20 weeks)

## ANAEMIAS (CDAs)

### Anaemia of prematurity

The haemoglobin concentration falls after birth in all babies but in premature infants it falls faster and to a lower level. At 1-3 months of age haemoglobin concentrations of less than 70 g/l are common and in babies born at less than 32 weeks gestation this anaemia is often associated with inadequate adaptive responses including tachycardia, tachypnoea and apnoeic attacks. The anaemia is due in part to shortened red cell life-span and the effects of rapid growth but the fundamental problem appears to be a poor erythropoietin response. Erythropoietin levels are highest in premature infants with the most severe anaemia and hypoxia but even in these cases levels are inadequate compared to those achieved in anaemic adults. Recombinant erythropoietin is of benefit in some infants.

### Polycythaemia in the neonate

Polycythaemia in the neonate is most simply defined as a packed cell volume (PCV) exceeding 0.7. Causes include placental transfusion (e.g. delayed clamping of the cord), intrauterine hypoxia, endocrine disorders (e.g. maternal diabetes) and genetic disorders (e.g. Down's syndrome). Significant polycythaemia may cause hyper viscosity with congestive heart failure, respiratory distress, neurological disturbances and even gangrene. Venesection with plasma replacement is indicated where a high PCV is associated with symptoms and signs of hyper viscosity.

### Thrombocytopenia in the neonate

Some causes of thrombocytopenia in neonates are listed in Table 3. In practice the major divide is between seriously ill infants where the low platelet count is caused by disseminated intravascular coagulation (DIC), and relatively well infants where thrombocytopenia is most often of immune aetiology or occurs secondary to a specific inherited syndrome. Idiopathic thrombocytopenic purpura (ITP) may be seen in infants born to mothers with ITP where there is passive transfer of IgG across the placenta. Alloimmune thrombocytopenia arises where the healthy mother becomes sensitised against a fetal platelet antigen in a manner analogous to HDN; the platelet antigen PI" is most commonly implicated.

### IRON DEFICIENCY IN INFANCY

Iron deficiency has already been discussed but some aetiological factors in infancy are unique to this period of life. Blood loss may still be the major cause of deficiency but other factors worthy of consideration are decreased total body iron at birth (e.g. prematurity, feto-maternal haemorrhage, twins), the impact of growth with increased demands for iron, and dietary inadequacy (e.g. excessive dependence on unsupplemented cow's milk).

### RED CELL APLASIA IN CHILDHOOD AND ADOLESCENCE

Pure red cell aplasia (PRCA) is characterised by anaemia, reticulocytopenia and reduced or absent erythroid precursor cells in the bone marrow. There are many causes of PRCA including infection (e.g. parvovirus B19), connective tissue disorders and malignancies (e.g. thymoma). However, two types of PRCA are unique to childhood: Diamond-Blackfan anaemia and transient erythroblastopenia.

### Diamond-Blackfan anaemia

This is a heterogeneous disorder. The majority of cases are sporadic but various patterns of inheritance have been documented. An anaemia with the features of red cell aplasia usually presents within the first twelve months of life. This runs a chronic course and can be combined with other anomalies and an increased risk of leukaemia and myelodysplasia. Beyond blood transfusion, therapeutic options include corticosteroids, androgens, immunosuppression, growth factors (erythropoietin, interleukin-3) and allogeneic bone marrow transplantation in severe cases.

### Transient erythroblastopenia of childhood

This is a transient form of red cell aplasia of probable immune origin which must be distinguished from Diamond-Blackfan anaemia. It generally affects older children (1-4 years) and may be diagnosed simultaneously in siblings or in seasonal clusters. In over half of cases there is a previous viral illness. The anaemia may be complicated by worrying neurological symptoms. Full recovery within 4-8 weeks is the rule.

### CONGENITAL DYSERYTHROPOIETIC

## Table 3 Some causes of thrombocytopenia in the neonate

DIC in various severe systemic disorders
Intrauterine infection (e.g. rubella, cytomegalovirus)
Platelet antibodies:
- autoimmune (maternal ITP)
- alloimmune
- drugs
- Hereditary / congenital disorders:
- Wiskott-Aldrich syndrome
- Thrombocytopenia with absent radii (TAR) syndrome
Post exchange transfusion
Neonatal leukaemia
Giant haemangioma

## Paediatric haematology

Chronic and severe blood disorders in children are usually best managed by a paediatrician with a special interest in haematology or in a combined paediatric/haematology clinic.

In haemolytic disease of the newborn (HDN), haemolysis is caused by maternal IgG antibodies crossing the placenta and attaching to fetal red cells. Most clinically significant cases affect a RhD positive fetus or newborn child where the mother is RhD negative.

RhD prophylaxis has much reduced the incidence of severe HDN.

Prematurity is associated with a particular type of anaemia.

In pure red cell aplasia in children it is important to distinguish between Diamond-Blackfan anaemia and the more benign transient erythroblastopenia of childhood.

## SYSTEMIC DISEASE

Clinical haematologists spend a considerable part of their time investigating blood abnormalities in patients with diseases of other organ systems. Some of the more common diagnostic challenges are discussed here.

### RENAL DISEASE

Diseases of the kidney are associated with a remarkably wide range of possible haematological abnormalities (Table 1).

Anaemia is almost inevitable in chronic renal failure. The pathogenesis is complex but impaired erythropoietin production is the principal cause. Other possible contributory factors include the release of inhibitors of erythropoiesis, mild haemolysis and iron deficiency. The anaemia of renal failure is typically normocytic and normochromic. A characteristic finding in the blood film is the presence of *burr cells* (Fig. 1). The best treatment of anaemia is resolution of the underlying renal problem (e.g. by transplantation), but where this is not feasible, recombinant erythropoietin is the treatment of choice. Intermittent bolus administration generally leads to a marked improvement in anaemia and transfusion independence.

A failure of the anaemia to respond to erythropoietin should prompt a search for other aetiologies such as iron deficiency.

Paradoxically, some forms of renal disease can lead to increased red cell production and clinical polycythaemia (Table 1). This arises either from inappropriate secretion of erythropoietin by a kidney tumour or from local renal hypoxia promoting erythropoietin release from normal cells. Polycythaemia can be the presenting feature of renal carcinoma and rapid identification of the malignancy may allow curative surgical treatment. Benign diseases such as polycystic disease and hydronephrosis probably cause polycythaemia by inducing renal ischaemia. The polycythaemia of renal disease is not an appropriate physiological response and patients with high-packed cell volumes (e.g. greater than 0.5) can derive benefit from regular venesection.

Chronic renal failure is also associated with a large number of possible platelet and coagulation abnormalities. The increased risk of bleeding in these patients is generally caused by the complex interaction of abnormalities shown in Table 1. Anaemia tends to worsen bleeding by interfering with the normal interaction between platelets and vascular endothelium.

### LIVER DISEASE

Advanced liver disease is often associated with abnormal haemostasis.

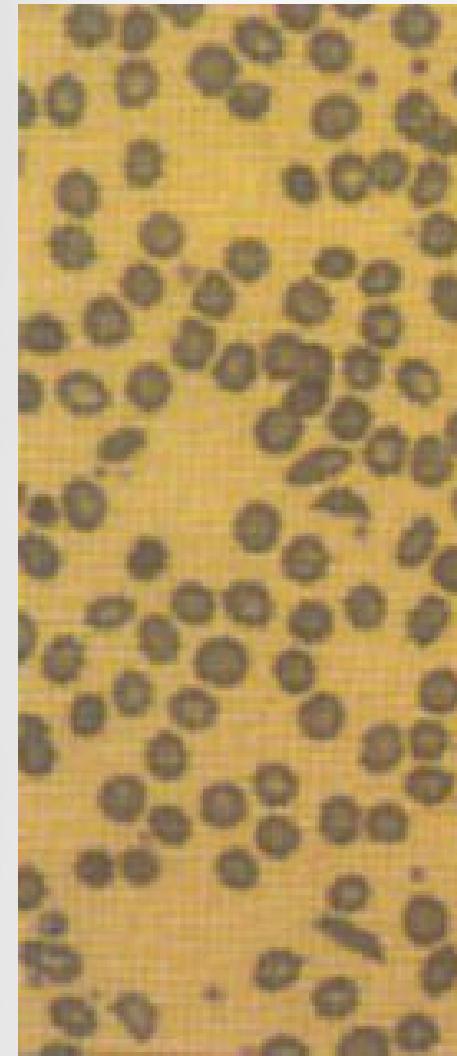
Table 1 Haematological changes in renal disease

Abnormality	Clinical association
Red cells	Anaemia Polycythaemia
	Chronic renal failure Renal carcinoma, cystic disease, hydronephrosis, parenchymal disease Bartter's syndrome, renal transplantation Renal failure
	Burr cells
Haemostasis	Abnormal platelet function Thrombocytopenia Disordered coagulation
	Renal failure

The complex coagulation abnormalities of renal failure usually lead to a bleeding tendency but nephrotic syndrome is associated with an increased incidence of thrombosis

### MALIGNANCY

Anaemia is seen in around half of patients with non-haematological malignant tumours. The anaemia of chronic disease is the most common aetiology but other causes include chemotherapy, blood loss, haemolysis and marrow infiltration. Invasion of the bone marrow by solid tumours can result in a pancytopenia and a characteristic leucoerythroblastic blood picture with circulating nucleated red cells and myelocytes (Fig. 2a). Clumps of



malignant cells may be seen in a bone marrow aspirate but a bone marrow trephine is a more reliable way of demonstrating solid malignancy (Fig. 2b).

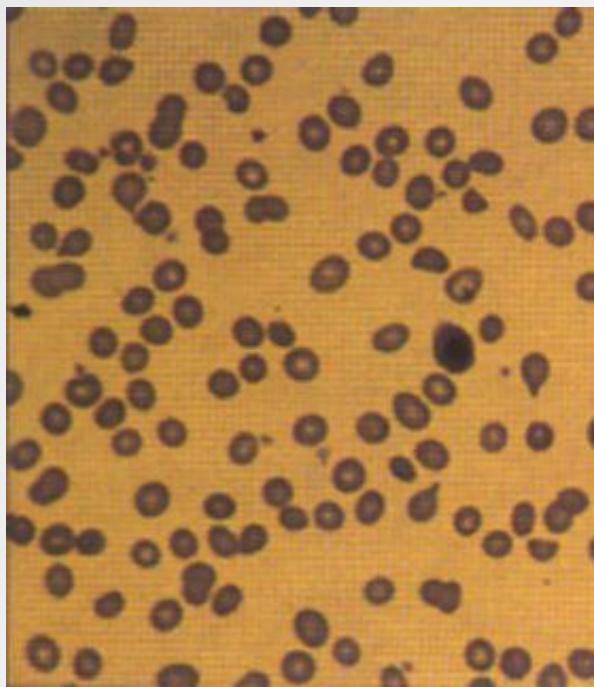
Malignancy can be associated both with a hypercoagulable state and a bleeding tendency. The presence of hypercoagulability was first suggested by the increased incidence of deep vein thrombosis and pulmonary embolism seen in cancer patients. The mechanism is thought to be activation of the normal clotting system with low-grade intravascular coagulation and secondary fibrinolysis. In the laboratory, common findings are elevated levels of clotting factors and a shortened prothrombin time and activated partial thromboplastin time. It is presumed that cancer cells secrete thromboplastin which initiates clot formation. Treatment of thrombosis in malignancy is difficult, as anticoagulant control is often poor. Antiplatelet agents such as aspirin and dipyridamole are a possible alternative approach both in treatment of established thrombosis and in prophylaxis.

Disseminated intravascular coagulation (DIC) can complicate malignancy. It may be an acute haemorrhagic state but is more often a chronic low-grade disorder with no bleeding. It is particularly likely to accompany carcinomas of the prostate, stomach, colon, breast, ovary, lung, gallbladder and melanoma.

Fig. 1 Burr cells in the blood in renal failure.

### CONNECTIVE TISSUE DISORDERS

Systemic disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and mixed connective tissue disease often lead to abnormal blood counts. In practice the most common finding, particularly in rheumatoid arthritis, is the anaemia of chronic disease. Immune thrombocytopenia is more often seen in SLE and this heterogeneous disorder may also be complicated by the presence of the lupus anticoagulant. Neutropenia can arise in several connective tissue disorders; the triad of long-standing rheumatoid arthritis, splenomegaly and neutropenia is termed Felty's syndrome. There may be a small increased risk of haematological malignancy in patients with rheumatoid arthritis. In Sjögren's syndrome there is a substantially



increased risk of nonHodgkin's lymphoma.

Fig. 2 Patient with prostatic carcinoma and invasion of the bone marrow. (a) Leucoerythroblastic blood picture: note the nucleated red cell.

(b) Bone marrow trephine specimen showing replacement of normal haematopoiesis by carcinoma.

#### INFECTIONS

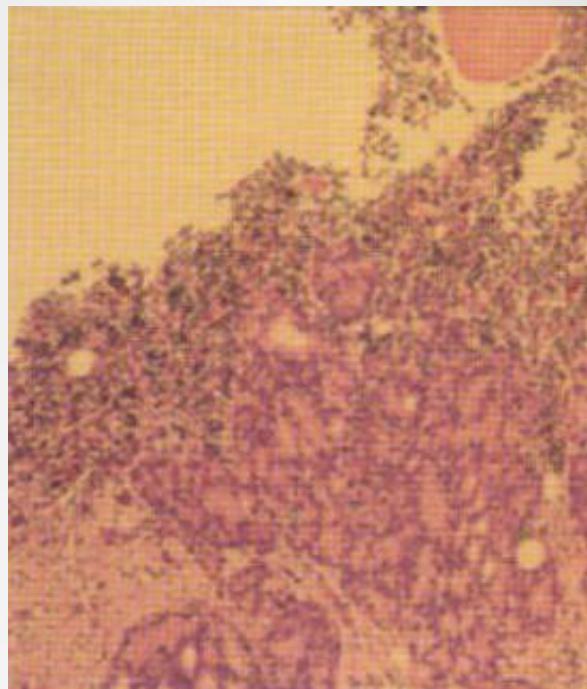
Infections are ubiquitous clinical problems in the community and hospital, and they are probably the most common cause of abnormal blood counts in a typical haematology laboratory. Different infections are associated with different abnormalities but it is possible to make some generalisations.

**Bacterial infections** commonly cause a neutrophil leucocytosis. The neutrophils are classically 'left-shifted' (i.e. reduced nuclear segmentation) with increased cytoplasmic granulation (toxic granulation). Very severe bacterial infections such as disseminated tuberculosis can induce a leukaemoid reaction with immature myeloid cells appearing in the blood.

**Viral infections** most commonly cause a transient lymphocytosis with reactive changes in the cells. Two types of viral infection merit more detailed description: infectious mononucleosis and HIV infection.

#### Infectious mononucleosis

Infectious mononucleosis (or glandular fever) is a disorder caused by the Epstein-Barr virus (EBV). It predominantly affects adolescents and young adults. Clinical features often include malaise, fever, pharyngitis, lymphadenopathy, splenomegaly and hepatitis. The haematological hallmark of the disease is the presence of numerous atypical lymphocytes in the blood (Fig. 3). These lymphocytes are mainly activated T-cells produced as an immunological response to EBV-infected B lymphocytes. Other possible blood changes are neutropenia, thrombocytopenia and a cold-type autoimmune haemolytic anaemia. The differential diagnosis is essentially other viral diseases, but where the blood abnormalities are severe the disease may be confused with acute lymphoblastic leukaemia. The diagnosis is confirmed by the Paul-Bunnell or Monospot tests which rely on the detection of



heterophile antibodies which appear in the serum. Treatment of infectious mononucleosis is essentially symptomatic, although corticosteroids can be helpful in unusually difficult cases.

#### HIV infection

Progressive HIV infection has many possible haematological consequences (Table 2). These result from a combination of a direct effect of the virus, opportunistic infection and side-effects from the drugs used in treatment. The blood changes are often similar to those seen in other viral infections but a chronic decline in the lymphocyte count is a particular feature. Examination of the bone marrow often reveals non-specific changes such as fibrosis, gelatinous transformation, trilineage myelodysplasia, increased lymphocytes and plasma cells, and prominent haemophagocytosis. The presence of granulomas can signify infection by atypical mycobacteria or other opportunistic pathogens. In clinical practice the major haematological problems associated with HIV infection are immune thrombocytopenia (ITP) and lymphomas. The latter are typically aggressive B-cell malignancies with extra-nodal involvement.

Fig. 3 Atypical lymphocyte in infectious mononucleosis.

#### Systemic disease

##### Table 2 Possible haematological changes in HIV infection

###### Blood Lymphopenia

###### Anaemia

- Neutropenia
- Thrombocytopenia
- Atypical lymphocyte morphology
- Anisopoikilocytosis
- Macrocytosis<sup>1</sup>

###### Bone marrow

- Variable changes in cellularity
- Gelatinous transformation
- Myelodysplasia
- Increased lymphocytes and plasma cells
- Increased fibrosis
- Opportunistic infection (e.g. granulomas)
- Lymphoma

###### Other

- Positive direct antiglobulin test (DAT)
- Lupus anticoagulant

Particularly in patients receiving the drug zidovudine

#### SYSTEMIC DISEASE

Renal disease can cause anaemia, polycythaemia and abnormalities in platelets and coagulation.

Malignancy often causes anaemia. Invasion of the bone marrow by solid turnout is a cause of a leucoerythroblastic blood picture.

Bacterial and viral infections are common causes of abnormal blood counts.

Infectious mononucleosis is a disease caused by the Epstein-Barr virus. Numerous atypical lymphocytes are seen in the blood.

The many possible blood changes of HIV infection result from a combination of a direct viral effect, opportunistic infection and drugs used in treatment.

## THE DEVELOPING WORLD

The term 'developing world' is used to describe the majority of tropical countries which are 'hot, humid and poor'. An alternative term is the 'less economically sound' nations, as these countries are often advanced in human and cultural resources.

Haematological practice is different to that in most developed countries. Genetic diseases such as the haemoglobinopathies and red cell enzymopathies are frequent in many tropical regions. Deficiency anaemia and haemolytic anaemia are often secondary to infections such as ancylostomiasis (hookworm) and malaria. Medical treatment regarded as routine in the developed countries is commonly unavailable. For instance, only about 20% of the world's haemophiliac population has access to factor VIII replacement therapy.

With the ever-increasing availability of 'exotic' holidays and regular foreign travel within immigrant populations, doctors in the developed world are seeing more tropical diseases. For the patient with unexplained symptoms such as malaise and fever, or signs such as splenomegaly, a history of travel should not be overlooked.

## MALARIA

Malaria is a protozoal disease, the infectious agent being *Plasmodium falciparum*, *P. vivax*, *P. ovale* or *P. malariae*. It is a growing health risk throughout the tropics and subtropics where insecticide resistance of *anopheline* mosquitoes and multiple drug resistance of malarial parasites have made control and treatment increasingly difficult. It has been estimated that worldwide one hundred million people are attacked annually with a mortality of around 1%, largely in children.

### Pathogenesis

The life cycle of the malaria parasite is illustrated in Figure 1.

When taking a meal of blood an infected mosquito initiates human infection by the inoculation of malarial sporozoites. These rapidly pass to the liver where they enter hepatocytes and divide. After several days, enormously increased numbers of parasites (merozoites) depart the liver and invade red cells. Here the merozoites develop via ring forms and trophozoites into schizonts. Rupture of the schizont releases 12-20 merozoites back into the blood thus perpetuating the cycle. The duration of the blood cycle varies between malarial species, explaining the different periodicity of fever in each type. A further mosquito becomes infected when it feeds on blood containing gametocytes, the sexual form of the parasite.

### Diagnosis

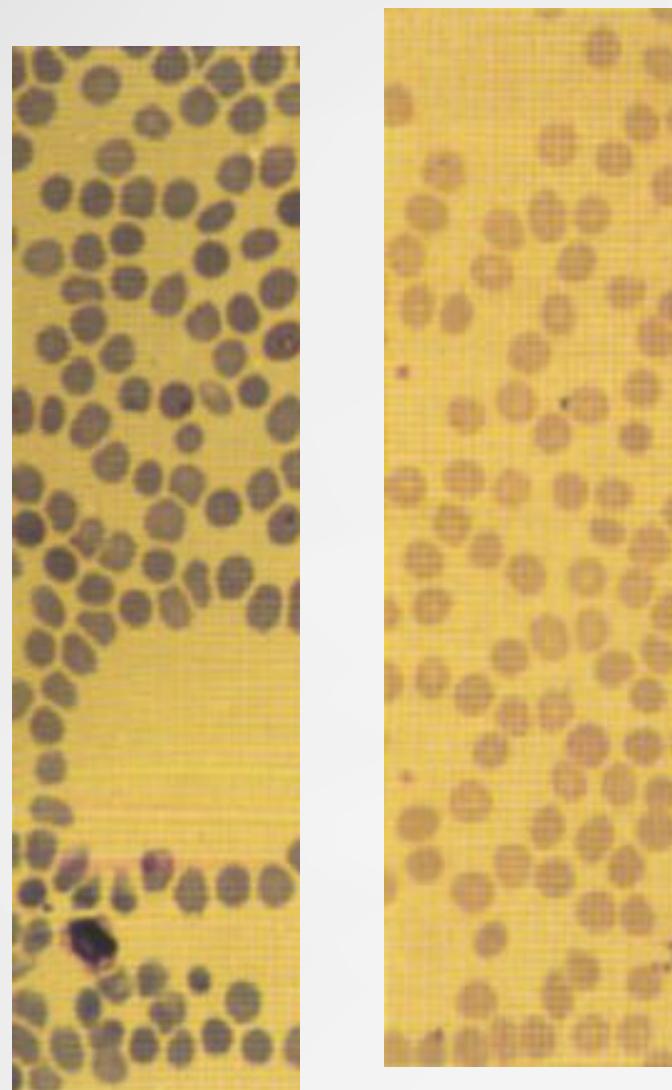
Although malarial parasites may be detected in normal blood films, their identification is generally easier in Leishmann or Giemsa stain at a higher pH. A thick film is best for detection and a thin film for determination of the species. Prolonged inspection of the film is sometimes necessary to spot malarial parasites as there can be a low level of parasitaemia. Where malaria is suspected on clinical grounds repeated samples may be needed to make or exclude the diagnosis. *P. falciparum* is often associated with higher parasite counts. Paradoxically, some very ill patients with malaria initially have no detectable parasites in the blood as there is sequestration of parasite-laden red cells in the tissues. An experienced microscopist will be able to identify the malarial species; it is beyond the scope of this book to make a detailed comparison of the four species but some typical appearances are shown in Figure 2. Other methods of parasite detection under evaluation include the quantitative huffy coat technique, antigen detection by monoclonal antibody and nucleic acid methods.

### Clinical features

Malaria has a different clinical presentation in non-immune and immune patients.

#### Non-immune patient

The interval between the mosquito bite and the onset of symptoms is typically one to two weeks. Common symptoms are rigors, sweats, headache, vomiting, diarrhoea and muscle pains. *P. vivax* and *P. ovale* are classically associated with bouts of fever on alternate days and *P. malariae* on every third day. Possible clinical signs include a rising temperature, tachycardia, herpes labialis, jaundice, dehydration and splenomegaly. *P. falciparum* infection is the most dangerous form of malaria. The onset can be insidious and the fever has no particular pattern. Life-



threatening complications such as cerebral malaria (with development of coma), acute renal failure and blackwater fever (rapid intravascular haemolysis), can suddenly develop in a patient previously not particularly ill. Children are particularly at risk of a sudden demise.

#### Endemic malaria

In indigenous populations, malaria presents variably depending on the degree of endemicity the age of the patient and the development of immunity. Thus in hyperendemic areas where there are seasonal variations, adults develop considerable immunity, malaria causing only short episodes of fever and a palpable spleen. In holoendemic areas there is infection through the year and

Fig. 2 Malarial parasites in the blood. (a) Ring-forms in *P. falciparum* malaria. (b) Schizont in *P. ovale* malaria. (c) Gametocytes in *P. vivax* malaria.

usually the disease manifests as a transient low parasitaemia with no symptoms. In hypoendemic areas, epidemics occur and the disease resembles that in the non-immune. *Tropical splenomegaly syndrome* is the development of massive splenomegaly in adults in hyperendemic areas. The patient has a low parasitaemia with an exaggerated immune response and very high levels of IgM.

#### Treatment and prophylaxis

Ill patients should be rested and rehydrated. A rational choice of drug treatment requires a knowledge of both the clinical syndrome and the likelihood of drug resistance. Chloroquine remains the choice for sensitive *P. falciparum* malaria. Quinine can be useful in areas of chloroquine resistance. Artemether, the active ingredient of a traditional Chinese remedy for fever, may be effective in quinine-resistant severe malaria. Patients with life-threatening complications of *falciparum* malaria require intensive medical support and prompt intravenous drug treatment. Chemoprophylaxis is advised for nonimmune travelers entering malarial areas. Chloroquine, proguanil and pyrimethamine have been widely used. Mefloquine may give the best protection in areas with chloroquine resistance. Where there is doubt, expert advice should be sought as all recommendations are constantly reviewed. Simple preventative measures protective clothes mosquito nets and insect repellent creams also help reduce the risk of infection.

#### VISCERAL LEISHMANIASIS (KALA-AZAR)

This protozoal disease is caused by the organism *Leishmania donovani*. It is a cause of massive splenomegaly. The organism may be detected in a blood film within monocytes or neutrophils but bone marrow aspiration is more sensitive.

#### OTHER PARASITIC DISEASES DETECTABLE IN THE BLOOD

These include the following:

**Filariasis.** Microfilariae are released into the blood during an acute attack of disease. As the organisms are motile, examination of a wet Preparation is useful.

**Babesiosis.** This tick-born disease only occasionally affects man. Trophozoites which resemble small ring-forms of *P. falciparum* can be found in red cells.

**Trypanosomiasis.** The parasites are extracellular and motile.

#### IRON DEFICIENCY IN ANCYLOSTOMIASIS (HOOKWORM)

Ancylostomiasis affects approximately 20% of the world's population. It is a major cause of gastrointestinal blood loss and iron deficiency anaemia in tropical regions. Worms attach to the upper small intestine and remove blood from the host; the daily loss can be as great as 250 mls. Management of anaemic patients should include both treatment of worms with an effective anti-helminthic agent and oral iron supplements to replenish stores.

#### ENDEMIC BURKITT'S LYMPHOMA

Endemic Burkitt's lymphoma is an aggressive B-lymphoblastic lymphoma which is found particularly in African children. In areas where malaria is holoendemic it is the most common childhood cancer. The disease is associated (EBV) infection with Epstein-Barr virus and the chromosomal rearrangement t(8, 14). The classical clinical presentation is with a massive tumour of the jaw or other extranodal disease. There is often a rapid response to chemotherapy but relapses are frequent and cure rates low.

The incidence of many haematological disorders and the availability of treatment is different in the developing world and developed countries.

Malaria is a protozoal disease transmitted to man by anopheline mosquitoes. It is a major health problem in tropical and sub-tropical regions.

Laboratory diagnosis of malaria depends on the identification of parasites in thick and thin blood films.

Optimum drug treatment of established malaria and the best choice of prophylaxis require expert knowledge of clinical syndromes and possible drug resistance.

Ancylostomiasis (hookworm) is a major cause of iron deficiency in tropical areas.

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## RECENT ADVANCES IN INVESTIGATION

An account of recent advances in the investigation of blood disorders must inevitably be dominated by molecular techniques and particularly the polymerase chain reaction. Flow cytometry has also found new applications and is briefly discussed.

### MOLECULAR BIOLOGY

#### OVERVIEW OF TECHNIQUES USED IN THE ANALYSIS OF DNA

##### **Southern blotting**

In this methodology, DNA is extracted from cells and then cut at specific sites by incubation with restriction endonucleases. The fragments of DNA are then separated out by electrophoresis prior to transfer to a nitrocellulose or nylon membrane by a blotting technique. DNA is then fixed to the membrane and specific sequences detected by the use of a radiolabelled probe. The method is relatively straightforward but time-consuming, taking at least seven days for normal analysis.

##### **Polymerase chain reaction (PCR)**

The advent of PCR has revolutionised molecular work in many medical specialities. Its rapidly increasing use is in part due to its unusual simplicity. The object of PCR is to amplify a preselected sequence of DNA many times over. This amplification greatly facilitates subsequent analysis of the DNA sequence for point mutations and polymorphisms, and often allows direct analysis of the product by gel electrophoresis without the use of probes. The method is shown schematically in Figure 1. Essentially two specific oligonucleotide primers are added to the DNA. These have sequences matching the regions flanking the region of interest. A DNA polymerase is added and the mixture heated causing the DNA to dissociate into two single strands. Following cooling the single strands bind to the oligonucleotides which are in excess. The oligonucleotide then acts as a primer for DNA polymerase and is extended to form a new double stranded molecule. With each repeat of the cycle the amount of DNA is doubled. Generally about 30 cycles are used and amplification of approximately  $10^6$  can be achieved.

##### **Fluorescence-in-situ-hybridisation (FISH)**

FISH describes the hybridisation of specific DNA or RNA sequences *in situ* to cellular targets attached to microscope slides. The most popular probes are chromosome specific DNA sequences which generate a brilliant signal in both metaphase and interphase nuclei. The technique is particularly useful in the demonstration of chromosomal monosomies or trisomies but chromosome translocations (Fig. 2), deletions and amplification of specific genes can also be detected.

#### APPLICATION OF MOLECULAR BIOLOGY IN HAEMATOLOGY

**Carrier detection and antenatal detection in genetic disorders** Molecular techniques now play a central role in genetic counseling and antenatal diagnosis in genetic disorders of the blood. Restriction fragment length polymorphism (RFLP) analysis is used as a method of tracking an abnormal gene in affected families. A major disadvantage of this approach is the necessity to study other family members. A PCR-based technique (mismatched amplification refractory mutation system or ARMS) can detect an abnormal thalassaemia gene; no gene product is obtained unless the primer corresponds to the mutated gene. In haemophilia A most gene mutations were thought to be private (i.e. only found in isolated families). However, a common inversion of the factor VIII gene has recently been identified in many haemophilia families. By southern blot analysis one or other of the two types of the inversion can be detected in around 40% of patients with severe disease. In these cases the inversion simplifies both carrier detection and antenatal diagnosis.

#### Haematological malignancy

##### **Diagnosis**

Leukaemias and lymphomas have traditionally been diagnosed on the basis of their morphological appearance and immunophenotype. In most cases a precise diagnosis is possible but on occasion there is doubt as to the lineage of the malignant cell or even as to whether the cell proliferation is malignant (i.e. clonal). In this context the development of probes for the immunoglobulin genes and T-cell receptor gene has been an advance. Firstly, a distinction can be made between B and T-lymphocyte malignancies. In almost all tumours derived from B-cells (e.g. BALL, BCCL, B-cell non-Hodgkin's lymphoma) a monoclonal rearrangement of immunoglobulin (Ig) genes is found, whereas in T-cell malignancies there is a corresponding rearrangement of the T-cell receptor (TCR) gene. Secondly, the presence of a clonal rearrangement of the Ig or TCR genes differentiates (with rare exceptions) a malignant proliferation of cells from a 'reactive' proliferation where the presence of many different rearrangements does not lead to the formation of specific bands on Southern blotting.

Where there are specific molecular markers of leukaemia (e.g. bcr-abl in CML, PML-RAR $\alpha$  in acute promyelocytic leukaemia) then molecular techniques are likely to play some part in diagnosis. They can be used to complement conventional cytogenetics and may provide additional information. The molecular abnormality can have prognostic significance: detection of the bcr-abl rearrangement in ALL indicates a low likelihood of cure by chemotherapy. It is less clear whether precise determination of the breakpoint within the breakpoint cluster region affects the prognosis in CML.

##### **Minimal residual disease**

Traditional definitions of remission in leukaemia rely on crude morphological criteria. Many patients in remission subsequently relapse implying the existence of occult neoplastic cells undetectable by normal morphological or cytogenetic methods - so-called *minimal residual disease* (MRD) (Fig. 3). Reliable detection of MRD would allow improved management with escalation of therapy for patients with persistent disease and the avoidance of excessive treatment in patients showing a good response to previous intervention. Now two techniques can detect MRD in selected disorders - immunological marker analysis (see below) and PCR. Successful use of PCR relies on the presence of a disease marker which can be targeted. Examples are junctional rearrangements of Ig and TCR genes, and chromosomal rearrangements defined at the molecular level, such as bcr-abl and PML-RAR $\alpha$ . Currently in the order of 10-45% of leukaemias carry a definable marker. Preliminary clinical studies suggest that early detection of MRD by PCR can predict later frank relapse, but larger trials are needed to establish its routine role in management.

##### **Bone marrow transplantation**

Molecular techniques can be used both to monitor MRD posttransplant and to improve the level of HLA matching between unrelated donors and recipients.

#### FLOW CYTOMETRY

##### **HAEMATOLOGICAL MALIGNANCY**

Immunophenotyping using a flow cytometer is a standard part of leukaemia diagnosis and classification. New ideas are under investigation. Detection of particular antigens on leukaemic cells may give useful prognostic information at presentation (e.g. presence of myeloid antigens on ALL cells). Multiparameter immunophenotyping enables the identification of leukaemia-associated phenotypes in many cases of acute leukaemia. This differentiation between leukaemic cells and normal progenitors allows monitoring of MRD. It is likely that the best strategy for detecting and monitoring MRD will be a combination of molecular and immunological methods.

##### **OTHER APPLICATIONS**

Flow cytometry is now a routine automated method for reticulocyte counting. In the blood transfusion laboratory the technology has a number of potential serological applications (e.g. detecting red cell bound Ig), and could also be used in the evaluation of haemolytic transfusion reactions, in predicting the survival of transfused red cells and in quantifying feto-maternal haemorrhage.

## RECENT ADVANCES IN TREATMENT

### Recent advances in investigation

Molecular biology techniques used in haematology in Southern blotting, the polymerase chain reaction (PCR) fluorescence in situ hybridisation (FISH).

Molecular techniques now play a key role in carrier detection and antenatal detection in genetic disorders such as thalassaemia and haemophilia.

In haematological malignancy, molecular techniques can aid diagnosis, distinguish between malignant and reactive cell proliferations, and improve detection of minimal residual disease (MRD).

Newer uses of flow cytometry include the detection of cells with leukaemia-associated phenotypes in acute leukaemia, automated reticulocyte counting and various serological methods in the blood transfusion laboratory.

This section addresses in more detail some recent developments in treatment previously alluded to in the coverage of specific diseases. Inevitably any listing of recent advances is subjective. Most clinicians would probably choose to emphasise developments in chemotherapy, the expanding role of growth factors and the imminent introduction of gene therapy for single gene disorders such as haemophilia and thalassaemia.

### CHEMOTHERAPY FOR HAEMATOLOGICAL MALIGNANCY: NEW APPROACHES

#### New agents

There are basically two approaches to the development of new drugs for the treatment of haematological (or other) malignancy. Large scale screening programmes evaluate considerable numbers of drugs with potential anti-cancer activity. Many promising agents have been identified with subsequent transfer into routine clinical practice. However, it is likely that this random approach will gradually give way to a second strategy where increased understanding of the cellular biology and biochemistry of cancer allows the rational design of drugs. Such agents will probably target specific stages of the malignant process within the cell.

DNA, the target of traditional drugs such as alkylating agents, is an attractive target for the next generation of chemotherapeutic agents. Antisense oligonucleotides are small synthetic nucleotide sequences complementary to specific DNA or RNA sequences which selectively inhibit the transcription or translation of a gene. They may be directed against particular oncogenes. Anti-bcr/abl antisense oligonucleotides have already been investigated as a means of in vitro purging of malignant cells from the bone marrow of patients with chronic myeloid leukaemia. Other oncogenes implicated in haematological malignancies (e.g. GMYC) may also be inhibited in this way. The delivery of these agents to malignant cells *in vivo* is problematic and may require the use of gene therapy strategies. Targets for anti-cancer drugs are not limited to the cell nucleus. Drugs may be designed to block malignant proliferation by selective inhibition of growth factors, cell surface receptors and intracellular molecules mediating transmission of signals from the membrane to the nucleus. Agents could target components of the second messenger cascade including tyrosine kinase and protein C. Other drugs could interact with membrane molecules involved in cell-cell or cell-matrix combinations crucial in local malignant invasion and metastases.

#### Peripheral blood stem cell transplantation (PBSCT)

Although novel drugs are under development, there remains dependence on more traditional cytotoxic drugs. One way to try and increase cure rates in haematological malignancy is to escalate the dose of conventional agents whilst designing strategies to minimise the inevitable toxicity. In this context, autologous PBSCT is a rapidly growing treatment modality. PBSCT has now largely superseded the use of autologous bone marrow in the support of patients receiving high-dose chemotherapy. The procedure relies upon the harvest of haematopoietic stem cells from the patient's blood by leucapheresis during the recovery phase from moderate doses of chemotherapy (Fig. 1). The growth factor GCSF is often used to facilitate this mobilisation of stem cells. The stem cell harvest is cryopreserved and is ultimately reinfused following the administration of high-dose chemotherapy.

The principle is the same as for autologous bone marrow transplantation but PBSCT has the advantage of giving more rapid recovery of a normal blood count than the traditional procedure. This translates into a shorter hospital stay, less dependence on antibiotics and blood products, and probably a reduction in the morbidity and mortality associated with high doses of cytotoxic drugs. In haematological practice PBSCT has been mainly used for younger patients with myeloma and lymphoma. Its use may be gradually extended to patients with chemotherapy responsive non-haematopoietic solid tumours.

#### Multi-drug resistance: possible solutions

The major problem in the treatment of leukaemia and other haematological malignancies is the emergence of cells resistant to chemotherapy. Genes capable of conferring resistance to cytotoxic drugs have been characterised. Of particular interest is the P-glycoprotein or multi-drug resistance gene (MDR 1), as its overexpression can lead to resistance to many of the agents used in the treatment of leukaemia. The MDR 1 gene encodes a membrane protein which acts as an ATP-dependent efflux pump transporting organic compounds out of the cell (Fig. 2). Elevated MDR 1 levels appear to be a poor prognostic factor in acute myeloid leukaemia. In an effort to overcome MDR a number of MDR-reversing agents have been given in conjunction with normal chemotherapy regimens. Cyclosporin

A is currently generating most interest with encouraging early results in myeloma and acute myeloid leukaemia refractory to chemotherapy alone.

#### OTHER APPROACHES TO THE TREATMENT OF HAEMATOLOGICAL MALIGNANCY

##### Differentiating agents: an isolated success

In most cases attempts to induce maturation of malignant cells have been disappointing. One remarkable exception is the drug all-trans-retinoic-acid (ATRA) in acute promyelocytic leukaemia (APL, the FAB M3 variant of acute myeloid leukaemia). Initial treatment with ATRA gives a high proportion of complete remissions without marrow hypoplasia. There is also a reduction in the incidence of the coagulopathy non-nally associated with this type of leukaemia. The clinical complete remission is usually accompanied by disappearance of the molecular marker of APL the PML/RAR $\alpha$  gene rearrangement. There is now evidence that induction of remission by ATRA followed by consolidation chemotherapy gives a significant survival advantage over the use of chemotherapy alone.

##### Alpha interferon: an expanding role

Alpha interferon is an anti-viral protein with immunomodulatory and anti-cancer activities. Its use in haematology generally exploits the latter attributes, although it has a role in chronic hepatitis C infection which affects many adults with severe haemophilia. For a lengthy period, interferon's main use was in hairy cell leukaemia. More recently the drug has become the treatment of choice for the majority of patients with chronic phase chronic myeloid leukaemia. The use of interferon as an adjunct to chemotherapy in myeloma and lymphoma also holds promise.

#### HAEMATOPOIETIC GROWTH FACTORS

Much in the early days of chemotherapy the precise indications for their use and the best dosages and combinations are gradually being worked out. GCSF and GM-CSF shorten the period of neutropenia following intensive chemotherapy with a resultant reduction in the number of infections and duration of stay in hospital. These agents can also be used to mobilise haematopoietic stem cells in the blood for subsequent harvesting (see above). More contentious is the inclusion of growth factors as an integral part of chemotherapy regimens to amplify the anti-leukaemic effect of cytotoxic drugs (e.g. combination of GCSF, fludarabine and cytosine arabinoside in acute myeloid leukaemia). G-CSF is given long-term in various forms of congenital or acquired chronic neutropenia to minimise the risk of infection. There is currently no effective platelet growth factor in routine clinical use but thrombopoietin (c-mpl ligand) is undergoing testing.

Immunological factors are important in preventing relapse of leukaemia after allogeneic bone marrow transplantation (see p. 55). Immunotherapy is therefore an attractive option for the treatment of leukaemia outside the transplant setting, particularly for the eradication of minimal residual disease. Several agents are being investigated (e.g. interleukin-2) but results to date are inconclusive.

#### GENETHERAPY

Gene therapy will be a major part of the medicine of the future. The principle is straightforward and illustrated in Figure 3. A new functional gene is inserted into a cell. Physical methods may be used (e.g. electroporation or liposomes), but most gene therapy to date has depended on viruses (usually retroviruses) as vectors of the gene. Current problems with this technology include the attainment of adequate expression of the new gene and the maintenance of this response for a prolonged period of time. There are also concerns regarding potential toxicity from the transfected DNA and viral vectors.

As single gene disorders, both thalassaemia and haemophilia are good candidates for cure by gene therapy. However, there are still sizable problems to overcome and it is likely to be several years before procedures are routinely performed for either of these diseases. Gene therapy's role in haematological malignancy is more speculative. The technique may eventually be used to insert informational drugs and cytokines into cancer cells or even to restore the function of defective tumour suppressor genes.

#### Recent advances in treatment

Recent developments in chemotherapy for haematological malignancy include the design of new drugs, peripheral blood stem cell transplantation (PBSCT) to escalate the dose of conventional drugs and the use of multi-drug resistance (MDR)-reversing agents.

Haematopoietic growth factors are increasingly used following chemotherapy to reduce toxicity and to mobilise stem cells for PBSCT

Gene therapy is likely to become the treatment of choice for single gene disorders such as haemophilia and thalassaemia. Its role in haematological malignancy is more speculative.

Haematology

## VENEPUNCTURE AND VENOUS ACCESS

Obtaining a sample of venous blood from a patient is the most commonly performed practical procedure in haematology. The technique is apparently straightforward but poorly performed venepuncture can both upset the patient and compromise the quality of the sample. Gaining venous access for the delivery of

fluids, blood c

### TAKING A VENOUS BLOOD SPECIMEN (VENEPUNCTURE)

The patient should be the correct patient - check their identity! Most serious haemolytic transfusion reactions arise from careless identification of patients and incorrect form labelling. Patients should sit or lie comfortably in such a way that no serious injury could result from a faint. The operator washes his hands and wears plastic gloves - insist on gloves that fit properly. The procedure is briefly explained to the patient. The presence of a little transient pain when the needle is inserted should be acknowledged but not exaggerated.

Under normal circumstances blood is most easily taken from a vein in the antecubital fossa; the median cubital vein is preferred (Figs 1 & 2). It is considerate to ask whether the patient is left- or right-handed and then to choose the non-dominant arm. A tourniquet is applied well proximal to the site. This should cause distension of the veins but not discomfort. Gentle palpation is the best method of identifying a vein and checking its patency. If a suitable vein proves elusive it may help to gently tap the area or to warm the arm in water. The skin over the chosen vein is thoroughly cleaned with antiseptic solution. Usually a 19 or 20 gauge needle is used but a smaller size (e.g. 21 or 23) can be used where the veins are fragile and in children. The syringe should be adequate for the sample - where larger blood samples necessitate more than one syringe a 'butterfly needle' may be preferred to a conventional venepuncture needle. The needle is inserted bevel uppermost along the line of the vein at an angle of around 20°. There is a distinctive 'give' as the vein is entered. Blood is aspirated into the syringe slowly to avoid haemolysis. The tourniquet is released and the needle withdrawn after a dry swab has been held to the site. Pressure should be applied by the patient or an assistant with the arm held straight or slightly elevated. The needle is removed from the syringe - not resheathed - and placed directly into a sharps container. The specimen is expelled gently from the syringe into the relevant bottles. Mixing with anticoagulant is best achieved by gently inverting the bottle several times - violent shaking will damage the sample. An adhesive plaster can be applied to the venepuncture site (check for allergy) when bleeding has stopped.

The above describes the procedure for a conventional needle and syringe. Increasingly, venepuncture is performed using closed evacuated container systems where a double-ended venepuncture needle is screwed into a holder and the evacuated tube inserted into the holder following entry of the vein. Blood is automatically aspirated into the tube as the vacuum is released. It is important to understand how the system works *before* undertaking venepuncture.

#### Precautions

Blood should not be taken from a vein proximal to an intravenous infusion as the sample can be diluted. Neither should eczematous or infected areas be used for venepuncture. If patients are known to have a blood transmissible infection (e.g. Hepatitis B or C, HIV) or are at increased risk of such an infection this must be indicated on the specimen bottle and request form. Due care must be taken as evidently this is sensitive information - special labels stating an infective risk are available. In view of the possibility of needle-stick injuries, those performing venepuncture should be vaccinated against hepatitis B.

#### Common problems

Venepuncture is not always easy. If blood is not aspirable following perceived entry of the vein it is worth withdrawing the needle slowly with suction applied as the vein may have been transfixed. If a vein cannot be located in the antecubital fossa it is permissible to use veins at the wrist or on the dorsum of the hand. If two attempts fail a more experienced colleague should be sought. As a last resort a sample can be taken from the femoral vein. The operator must be familiar with the anatomy of the femoral region as the vein lies close to the femoral artery and nerve.

#### Children

In babies and infants a blood sample is often more easily obtained from a stab wound made with a lancet (capillary blood). The usual site is the heel, although fingers and earlobes can be used. Venepuncture may also be from scalp veins.

### VENOUS ACCESS

#### Peripheral venous cannulation

Almost all haematology patients admitted to hospital require at some stage a drip to infuse fluids, blood products or drugs. Before inserting a cannula into a vein, an appropriate giving set should be prepared in accordance with instructions and the bag or bottle containing the infusion fluid inverted and hung on the drip stand. The set should be properly primed and all bubbles excluded. The operator must wash hands and wear gloves. It is vital to ensure that the patient is comfortable and fully understands the procedure. The choice of cannula depends both on the quality of the veins and the duration and type of infusion. For short-term infusions or small veins a winged metal cannula (butterfly needle) is often suitable. In other circumstances a larger gauge plastic cannula is used (Fig. 3). An 18-gauge cannula is appropriate for crystalloid solutions but a 14- or 16-gauge is needed for blood.

The best site is the non-dominant forearm or the dorsum of the hand. The antecubital fossa is best avoided as it is uncomfortable to have the elbow immobilised. A tourniquet is applied and the skin cleaned as for venepuncture. The skin at the site may be stretched slightly to immobilise the vein. The cannula assembly (metal needle and surrounding plastic cannula) is introduced through the skin and into the vein. Once blood enters the cannula chamber or is easily drawn into a syringe, the tourniquet is released and the metal needle withdrawn from the plastic cannula which may be advanced further into the vein.

The pre-prepared giving set is attached to the cannula and fluid allowed to enter the vein whilst the insertion site is carefully inspected for possible extravasation. The needle is promptly disposed of in a sharps receptacle. To minimise the chance of the drip being infected or dislodged the site is protected with a sterile dressing and the cannula secured with a bandage or adhesive tape. The most common problem is failure to locate a vein in the favoured sites. A more experienced operator (e.g. an anaesthetist) may be successful. Where problems persist in experienced hands, other veins such as those in the region of the ankle or the subclavian, jugular or saphenous veins may be cannulated. Regular inspection of the drip site and careful hygiene will minimise the chance of infection. Where there is local inflammation or an otherwise unexplained bacteraemia, the cannula should be removed and another site used.

#### Central venous cannulation

Insertion of wide lumen silicon rubber catheters (generally referred to as Hickman catheters) is routinely undertaken in clinical haematology where recurrent intravenous access is required. Examples include:

- patients with haematological malignancy receiving intensive chemotherapy
- patients with thalassaemia having regular blood transfusions
- children with haemophilia A on prophylactic factor VIII treatment.

The catheter is normally inserted into the subclavian vein and the location of the distal tip checked on X-ray (Fig. 4). The proximal end of the catheter can be tunneled under the skin with an exit site on the anterior chest wall. A catheter cuff within the tunnel promotes the formation of fibrous tissue which helps secure the device. The procedure is usually performed in the operating theatre by a surgeon or anaesthetist. Once in place the catheter may be used for several months. Strict aseptic technique is necessary as infection with coagulase negative staphylococci is the most common complication.

#### Venepuncture and venous access

Obtaining a venous blood sample (venepuncture) is a commonly performed practical procedure in haematology; poor technique can upset the patient and ruin the sample.

In babies and infants, capillary blood sampling is often easier than venepuncture.

Peripheral venous cannulation is commonly performed to infuse fluids, blood products and drugs.

Where there is serious difficulty in locating a vein for venepuncture or cannulation, more experienced help should be sought.

For recurrent venous access, insertion of an indwelling central venous catheter can be helpful.

## BONE MARROW ASPIRATION AND TREPHINE BIOPSY

The indications for performing bone marrow aspiration and trephine biopsy procedures have previously been discussed. In this section the practical aspects of obtaining these samples are outlined. More detailed accounts can be found in books of practical procedures, but ultimately the only way to perfect technique is to practise under expert supervision.

Although the anterior iliac crest is occasionally preferred, most operators get the best specimens from the posterior iliac crest. The sternum is now less frequently used. This is, in part, due to the small risk of causing catastrophic damage to the mediastinum, but mainly because it is not possible to obtain a trephine biopsy. Only the posterior iliac crest approach is described here.

### BONE MARROW ASPIRATION

As for all procedures the sequence of events should be explained to the patient and reassurance given. A degree of discomfort should be acknowledged but it should be emphasised that this is transitory. In most adults, local analgesia is adequate but sedation is considered where patients are unusually anxious. A general anaesthetic is the norm in children. A clean, no touch technique is mandatory and most operators now wear gloves. Stringent asepsis is needed in immunosuppressed cases.

The patient lies in the left or right lateral position and the skin over the posterior iliac crest is cleaned with antiseptic prior to screening with sterile drapes. The crucial next stage is to properly identify the bony landmarks (Fig. 1). This is straightforward in most patients but can be problematic in obese subjects. If there are real difficulties in locating the posterior iliac crest then the anterior crest or the sternum may be considered. A local anaesthetic (normally 1 or 2% plain lignocaine) is infiltrated into the skin and then down to the periosteum. The Salah aspirate needle is shown in Figure 2. Before use it should be checked that the stylet is easily withdrawn and the guard is removed (this is only required for sternal aspirates). The needle is inserted through the skin and subcutaneous tissues at the site of lignocaine infiltration until the periosteum is encountered. It is pushed through the periosteum with a deliberate screwing motion (alternating clockwise and anti-clockwise) - a 'give' is felt as the marrow cavity is entered. The stylet is withdrawn and a syringe attached to the needle (Fig. 3). Approximately 1 ml of marrow is aspirated into the syringe. The patient should be warned that this stage often causes pain but that it is momentary. Marrow aspirate smears must be made promptly at the bedside before the marrow clots. If a larger volume is needed for tests such as cytogenetics and immunophenotyping, it is best to use a second syringe as large samples dilute the marrow with peripheral blood and reduce the quality of the morphological preparations. If it proves difficult or impossible to aspirate marrow it is worth replacing the stylet and carefully advancing or retracting the needle a short distance before repeating aspiration. It is important to remember that a 'dry tap' can result from marrow pathology (particularly fibrosis or solid malignancy) and is not always caused by poor technique.

Once the aspirate needle is withdrawn, firm pressure is applied to the site for a few minutes and then a sterile dressing or plaster used as protection. The patient lies on his/her back for 15 minutes to ensure a period of recuperation and further light pressure is applied to the puncture site. Outpatients should probably be observed for at least an hour before being allowed home (evidently more if sedated). Troublesome haemorrhage from the site is rare but it is sensible to correct a severe coagulation defect before undertaking the procedure. Thrombocytopenia alone is generally not a problem.

Patients often ask how quickly the 'results' will be available. Aspirate slides can be processed for microscopy within a few hours but most ancillary tests (see Table 1) take longer.

Table 1 Ancillary tests which may be performed on bone marrow aspirate samples

- Cytchemistry
- Cytogenetics
- Immunophenotyping
- Molecular studies
- Microbiological culture
- Cell culture studies

### BONE MARROW TREPHINE BIOPSY

In practice the trephine procedure is usually performed immediately following the aspirate at the same site. It is helpful to enlarge the aspiration puncture site slightly with a scalpel blade. There is more prolonged discomfort than in the aspirate procedure and sedation is indicated in anxious adults, and a general anaesthetic is necessary in children. A number of different needles are available - the Jamshidi type is illustrated in Figure 4. Smaller needles are available for paediatric use.

It is important to ensure that the device is complete and that the stylet can be easily withdrawn. The trephine needle is inserted in a similar fashion to the aspirate needle through the periosteum and approximately 1/2 cm into the cortex - when properly inserted the needle should easily support its own weight (Fig. 5). The stylet is removed prior to advancing the needle 2-3 cm using the same oscillatory movement. The needle is aimed towards the anterior iliac crest. The method for breaking off the biopsy varies with the needle used. For a Jamshidi needle the usual technique is to cut the core off by carefully withdrawing the needle a few millimetres and then readvancing the same distance in a different direction. The needle is then withdrawn taking care not to catch the skin and lose the biopsy in subcutaneous tissue. A special blunt probe is provided to push the biopsy out of the needle. The probe is inserted (with great care to avoid injury to the operator) at the sharp end of the needle so as not to traumatise the sample.

If the aspirate is a 'dry tap' it is worthwhile gently dabbing the trephine biopsy onto a glass slide before putting it into histological fixative. This 'touch preparation' is not useful for subtle morphological diagnosis but can permit rapid identification of malignant infiltration. It usually takes several days to process the trephine biopsy. Aftercare is the same as for the aspirate, although as it is a slightly more invasive procedure the patient also having a trephine may require a longer period of recuperation. Nevertheless, trephine biopsies are routinely performed in the outpatient clinic.

### BONE MARROW HARVESTING

Bone marrow can be harvested from a patient (for autologous bone marrow transplantation) or from a donor (for allogeneic bone marrow transplantation). The procedure is performed under a general anaesthetic, the marrow being collected from the iliac crests using multiple punctures with specialised harvest needles. Normally, approximately one litre is harvested from an adult in under an hour. Donors are hospitalised for around 48 hours. Serious side-effects are rare but some short-lived discomfort over the aspiration sites is common.

#### Bone marrow aspiration and trephine biopsy

The optimal site for both bone marrow aspiration and trephine biopsy procedures is the posterior iliac crest. Local analgesia is often adequate but nervous adults require sedation and children normally require a general anaesthetic.

Marrow aspiration smears may be stained for microscopy immediately after the procedure whereas trephine biopsies are processed over several days.

Serious side-effects from posterior iliac crest aspiration and trephine biopsy are very rare. Occasionally there can be excessive haemorrhage or local infection at the site.

Bone marrow can be harvested from the iliac crests in patients (for autologous bone marrow transplantation) or healthy donors (for allogeneic bone marrow transplantation).

# HEART ATTACK

## How to Prevent One

**Examining a live sample of your blood can reveal whether you're prone to a heart attack—and show you how to prevent it from ever happening.**

BY JAMES R. PRIVITERA, M.D.

**S**uppose you think you're prone to a heart attack or have health factors suggesting the possibility of one, there is a simple, inexpensive way to "ask" your body if conditions exist to make a heart attack possible. Even better, once you know your level of risk, it's easy to take preventive steps, using nutrition, to keep it from ever happening.

The simple, inexpensive technique is called darkfield live blood microscopy. We draw a drop of your blood from your fingertip and place it on a microscope slide. Then a special lens inside the microscope projects an intimate view of your living blood onto a television or computer screen by way of a video camera. A Polaroid camera is hooked up to the device enabling us to take photographs of a patient's blood condition before and after treatment. The result is a living picture of the cellular you.

**WHAT SILENT CLOTS CAN DO WITHOUT WARNING**  
The advantage of using a darkfield microscope instead of the more conventional brightfield is that we can see much more detail, such as the contours and shapes of red blood cells and platelets. In a cubic centimeter of blood from a healthy individual, there are usually close to 300,000 platelets, which are disc-shaped elements essential for blood clotting.

### Biofeedback Klinik

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Biofeedback Technician

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mkovacs@vastore.com

Quantum X-ray (QXR), a new healing Paradigm



the movement of the red blood cells through a capillary (which is a tiny, tributary blood vessel) and block them from releasing oxygen to the tissues. This means you will have a lower oxygen concentration in your blood, a clinical condition called ischemia (iss-KEY-mee-uh).

The biggest problem about blood clotting inside your blood vessels is that you probably will have no idea it's happening. When patients come to the office with chest pains (a strong indication of risk), I immediately have a look at their blood. But about 80% of heart attacks are painless, which means the ischemia due to blood clotting produces no pain or gasping and therefore gives you no warning.

You may be driving the car and suddenly slump over the wheel with a silent heart attack. This frightening event may be prevented through a darkfield examination of your blood, followed by a precise nutritional prescription to reduce platelet aggregation. In the darkfield blood pictures [see left], the platelet cluster looks like a blob of oatmeal poured onto a black surface. This is what blood clotting looks like, and it's also the face of a condition that could produce a heart attack.

### HOW CARLON AVOIDED A TRIPLE BYPASS SURGERY

Carlon, aged 62, came to me with high blood pressure (170/70), chest pains, and a 5-year history of serious heart problems, including a moderate heart attack. He had undergone numerous mainstream treatments, which hadn't helped him, and now his conventional physician was urging him to have triple-bypass surgery.

"A total of 14 doctors of the highest degree told me I couldn't live without this surgery, that it was imperative," Carlon reported. "They all agreed that this was the 'only' way they had to keep me alive."

They told him if he didn't have the surgery in 2 weeks or less, he would probably die.

Carlon didn't buy this pessimistic forecast and refused the surgery. He came to me for help. "I believe God built a cage over my heart for a reason. It doesn't need to be messed up with a knife," said Carlon.

I performed a comprehensive mineral analysis from a sample of Carlon's hair, and a darkfield examination of his blood. He was seriously low in selenium, magnesium, zinc, chromium, and manganese, and he had some large clots which, incidentally, are associated with a magnesium deficiency. My treatment program for Carlon had 2 major aspects: chelation therapy and a nutritional prescription.

First, Carlon started having intravenous chelation twice weekly to improve his circulation and remove heavy metals from his system.

**Chelation therapy** is a clinically proven method of binding up ("chelating") and draining toxins and metabolic wastes from the body while at the same time increasing blood flow and removing arterial plaque. In chelation, a nontoxic sub-



See Heart Disease, pp. 71-74; Hypertension, High Blood Pressure, pp. 725-728; Chelation therapy, pp. 126-133; Nutritional Supplements, pp. 383-397.



DEFINITION

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## How You Rot & Rust

At the physical level, disease and aging of the body is all about rotting and rusting. The rot is an underlying biological mechanism inherent in all earthly species and the rust is an oxidative process. Here we present some core education with out-takes from our pre-training workshop. Because the concepts build on each other, it is helpful to take the Rot & Rust "tour" one page at a time starting at the beginning. When you get to the end of the page you can just click on to the next.

### The Argument that Changed the Course of Medicine.

#### Pasteur vs. Bechamp

Non-changeable microbes cause disease. Monomorphism. The Germ Theory.

Microbes change. How - function of terrain. Pleomorphism. Terrain (toxicity) Theory.

Ultimately, Pasteur won, but reversed himself on his deathbed....

**“...the microbe is nothing, the terrain is everything.”**

Unfortunately...

The road was paved for the germ theory and it was too late for medicine to turn around.

**Result Medicine of today alleviates symptoms of disease, but rarely the cause.**

## All illness is but one constitutional disease

### - result of mycotoxicoses.

(Toxicity brought about by mycotic infection, i.e. yeast and fungus infection, the great decomposers of life.)

Understand this,  
understand disease.

Blood is not a sterile environment.

Idemiatology

**How you Rot and Rust THE BIOLOGY OF DISEASE** We have, living within our blood, colloids of life. The colloids of life are what Enderlein called the protit. Colloids are particles that measure .01 to .0001 microns in diameter (that's about 4 hundred thousandths to 4 millionths of an inch.) There is some point in space and time where the colloids of life (the smallest of biological living particles in the physical realm) were beget from the colloids of light (the spiritual realm). The first individual to actually catch a glimpse of this occurrence was Anton Leeuwenhoek who lived in the 17th century. He had ground glass to create the first microscope. In observing some rainwater he collected, he made note that there were teeny creatures moving about. Wondering where they came from, he did an experiment. He collected clean fresh rainwater and sealed it in pipettes. At first, nothing was in the water. Hours and a few days later, nothing still was in the water. But on the fourth day, all of a sudden, little teeny creatures appeared. Where did they come from? It was spontaneous generation. Life out of light. Leeuwenhoek took his research to Robert Boyle, the father of chemistry as we know it, and to Sir Isaac Newton who wrote many of the principles of physics. They did not believe that life could beget from light or in their way of thinking, from nothing. This was a time when the church played a big role in every major decision that was made. To have life you must have procreation, a mother-father union. Since there was no mother or father that created Leeuwenhoek's teeny creatures, his observations were surely flawed, and they were dismissed. What could not be dismissed however was the observation of a newly discovered microscopic world. It was a foundation for developing the beginning ideas of the germ theory. But what the germ theory failed to explain then, and fails to explain to this day, is the question; from where exactly do germs come? Where is the mother-father microbe? In any textbook of science, medicine or biology, there is no explanation. When the germ theory took hold in the early years of biological science, the religious dogma of the time shaped the scientists thoughts who formulated the theories. Since they had no concrete evidence to answer the question, they left it unanswered. And it remains unanswered today. And this is where a new paradigm unfolds. *Germs and microbes are physical life forms. Life forms which have evolved from something. Since that*

something is not physically measurable, then it must be something that is on a higher vibrational or spiritual level. Hence, colloids of light, which beget the colloids of life. For an empirical scientist, speaking about colloids of light is akin to speaking mumbo-jumbo. How can there possibly be a spiritual or higher vibrational particle of existence (which for lack of better understanding I've called a colloid of light) which is unseen and unmeasurable? And how can a supposed colloid of light become a colloid of life? In answer to the first question, the truth of the matter is, empirical science only goes as far as the current state of physical technology allows. To go beyond you have to turn to inner guidance, intuition, and quite frankly, to a quantum physical or spiritual perspective. Regarding the second question, how can colloids of light become colloids of life, doing an experiment can help to find an answer. From the writings of Dr. Kurt Donsbach, he calls this experiment, "making protozoa". The protozoa is among the most primitive and simplest life forms. In any biology textbook, you'll never find a description of where protozoa come from, but yet you can create them in a test tube. If you take sterile water, and put in some fresh hay or other grasses, then mix it up, you will have a solution that upon microscopic examination, has nothing in it. You can scrape the blades of grass with a knife and observe the scrapings and you will still find nothing. But cork the tube, wait a few days and come back. Your mix will be teeming with bacteria, amoebas and protozoa. Where did they come from? Under time-lapse photography, you would observe an amazing transformation. The grass would lose their striations and become more vesicular (filled with little bubbles or vacuoles). The vacuoles would begin to merge and gradually form a common membrane. After a few days the little mass begins to move with a rhythmic pulsing motion. Eventually the pulsing motion becomes more pronounced and the glob appears to gather more energy. Soon it breaks away from the grassy shaft and is a living mass, classified in biology texts as protozoa. From this point it can differentiate itself and other microorganisms appear. Fascinating isn't it? Just what was that preprotozoan mass pulsing with? Is it the beginnings of life? Could it be what's called the Life Force, or Prana, Chi, Eck, the Holy Spirit? The higher vibrational essence of spirit - the spark of God? Colloids of light - the spiritual, higher vibrational "stuff", beget the colloids of life - the physical manifestation of animate material substance. And just as in our protozoan experiment, we find that **the colloids of life have an urge to merge**. How they merge, what they turn into, their developmental function, all will be dependent upon the terrain or the environment to which they are exposed. Voila, we've just uncovered the pleomorphic theory. Microbes change based upon the environment in which they live. The human body strives to maintain the pH of the blood around 7.3. Above or below this level and the colloids of life in your blood merge into forms that may not necessarily be to your advantage. They can become pathogenic microbes. At one stage of development, the forms created by the colloids of life in the blood serve a useful function. Pleomorphic biologists have discovered that blood platelet formation is one example. Platelets are formed out of the colloids of life in the blood and serve us through the blood clotting mechanism, a mechanism without which we would bleed to death from even the smallest injury. But, just as the colloids of life

that form platelets serve us well, if the terrain of our blood is shifted due to an inverted way of eating and living, even platelets themselves can change their shape, or clump together, or become pathogenic. (More on these concepts later.) The colloids of life can take shape in millions of ways, specifically how and to what form is dependent on their environment. From bacterial, to viral, to fungal - the microbial changes, when it begins happening in your body, is one mechanism through which you age, become diseased, die, and ultimately are returned to the colloids from which you were assembled - as "from dust you are and from dust you shall return." The microscope is an incredible tool to delve into this world and educate oneself on the disease process. By looking at live blood immediately after taking it out of a finger, the life forms in the blood become apparent. What forms you see, depend on your state of health.

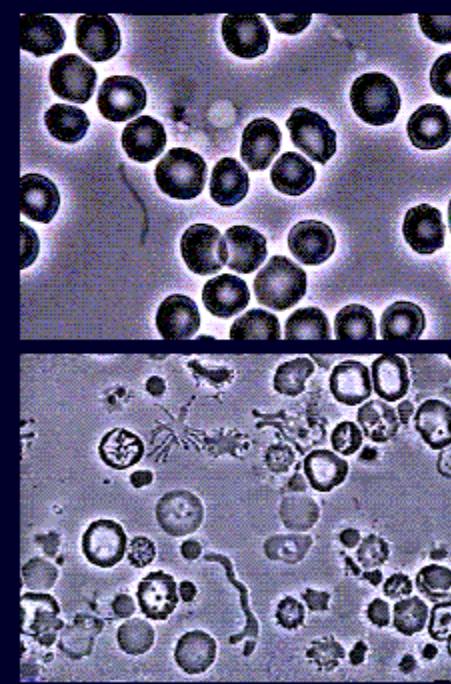
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Blood pH  $< > 7.3$  means terrain change, the colloids in the blood (the blood microbes) change, possibly becoming pathogenic.

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## Symbiotic Relationship

But Beyond this narrow symbiosis, lies potential microbial anarchy.



Above are two views of live blood as seen with a video microscope. The picture on top shows 1) the red blood cells floating in plasma. 2) a pleomorphic microbe known as a synascit (the wormy looking thing) which is often associated with a present or pending degenerative disease situation. 3) white round

bacterial forms often called "yeast" which should not be present in healthy blood.

4) An L-form bacterial variant around a platelet; pleomorphic biologists understand these forms to be dry protein organizations based on the direct fusion of living colloids (termed systatogeny). The patient with this blood had periods of fatigue and low energy, nothing specific diagnosed, though presence of a synascit is suspicious. The picture on the bottom is from a patient diagnosed with inoperable cancer and given 30 days to live by her doctor. This picture was taken approximately 40 minutes after taking the blood from the finger. The plasma field and red blood cells (what's left of them) are filled with pleomorphic microbes. Ashes to ashes and dust to dust, the microbes are starting to do their job and overtake the body. **An Interesting Case History**

The picture of blood above of the cancer patient leads to a pertinent story. The story involves how this patient came about getting her cancer into remission. She was diagnosed as inoperable and her medical doctor told her because of her very poor state of health, there was nothing more they could do. They suspected she had maybe 30 days to live. At the time her husband had been seeing an alternative care practitioner for a problem of his own. This particular doctor happened to work with a microscope in his practice for patient education. As a last ditch effort the man brought his wife in, hoping that maybe something, anything, could be done. As they sat in the office, she had such low energy, she could barely keep her head held up. Her face was completely white. As the blood was taken from her finger and put under the microscope, the doctor peered into the eyepiece. What he saw, or more to the point, what he didn't see, astonished him. The woman had practically no red blood cells, and what she did have, didn't look very good. There were pleomorphic microbes all over the place. Given the situation, where here is a woman that is next to dead, what can you do? Well, the doctor said he didn't know if it would help, but he pulled four key nutritional substances off his shelf and gave them to her. These were; a total vitamin and mineral complex, digestive enzymes, a proanthocyanadin (pycnogenol) antioxidant compound, and heavy duty metabolic body enzymes. After a little bit of talking about these substances and nutritional concepts, the couple left the office. When the doctor peered into the microscope after they left, which was about 30 to 40 minutes later, he couldn't believe his eyes. The parasitic creatures were everywhere, consuming everything left in the blood. The picture on the previous page is some of what he saw. One week after taking the nutritional supplements, the woman had renewed energy and was actually feeling better. She went back to her traditional doctor and wanted to have a blood test. The test was performed and her red blood cell count had shot up dramatically. The doctor was rubbing his hands together thinking that now they could re-start her on something like chemotherapy. She said something to the affect of "no thanks doc, I just wanted another opinion, adios. Since the hospital had essentially given her up for dead, she didn't want anything to do with them or with their killer medicines. With her renewed energy and new hope, she started seriously looking at alternative treatment options. She settled on a course of action and found a more sane approach to her condition south of the border in Mexico. 90 days later she was doing fantastic as her cancer was well in

remission. What got her to turn the corner? An alternative health care practitioner with a microscope that understood the importance of key nutritional elements to the body. The body is such an incredible thing that if you work with it correctly, instead of against it, it is capable of tremendous self healing.

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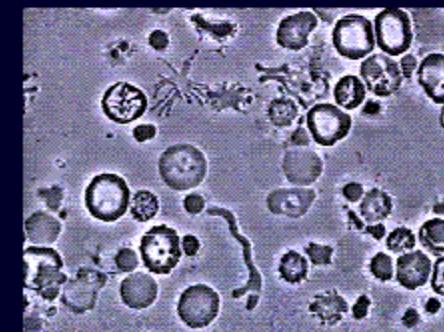
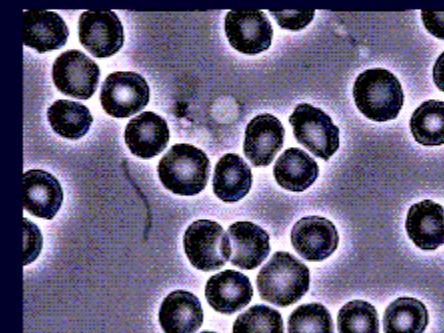
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Above are two views of live blood as seen with a video microscope. The picture on top shows 1) the red blood cells floating in plasma. 2) a pleomorphic microbe known as a synascit (the wormy looking thing) which is often associated with a present or pending degenerative disease situation. 3) white round bacterial forms often called "yeast" which should not be present in healthy blood. 4) An L-form bacterial variant around a platelet; pleomorphic biologists understand these forms to be dry protein organizations based on the direct fusion of living colloids (termed systatogeny). The patient with this blood had periods of fatigue and low energy, nothing specific diagnosed, though presence of a synascit is suspicious. The picture on the bottom is from a patient diagnosed with inoperable cancer and given 30 days to live by her doctor. This picture was taken approximately 40 minutes after taking the blood from the finger. The plasma field and red blood cells (what's left of them) are filled with pleomorphic microbes. Ashes to ashes and dust to dust, the microbes are starting to do their job and overtake the body.

**An Interesting Case History** The picture of blood above of the cancer patient leads to a pertinent story. The story involves how this patient came about getting her cancer into remission. She was diagnosed as inoperable and her medical

doctor told her because of her very poor state of health, there was nothing more they could do. They suspected she had maybe 30 days to live. At the time her husband had been seeing an alternative care practitioner for a problem of his own. This particular doctor happened to work with a microscope in his practice for patient education. As a last ditch effort the man brought his wife in, hoping that maybe something, anything, could be done. As they sat in the office, she had such low energy, she could barely keep her head held up. Her face was completely white. As the blood was taken from her finger and put under the microscope, the doctor peered into the eyepiece. What he saw, or more to the point, what he didn't see, astonished him. The woman had practically no red blood cells, and what she did have, didn't look very good. There were pleomorphic microbes all over the place. Given the situation, where here is a woman that is next to dead, what can you do? Well, the doctor said he didn't know if it would help, but he pulled four key nutritional substances off his shelf and gave them to her. These were; a total vitamin and mineral complex, digestive enzymes, a proanthocyanadin (pycnogenol) antioxidant compound, and heavy duty metabolic body enzymes. After a little bit of talking about these substances and nutritional concepts, the couple left the office. When the doctor peered into the microscope after they left, which was about 30 to 40 minutes later, he couldn't believe his eyes. The parasitic creatures were everywhere, consuming everything left in the blood. The picture on the previous page is some of what he saw. One week after taking the nutritional supplements, the woman had renewed energy and was actually feeling better. She went back to her traditional doctor and wanted to have a blood test. The test was performed and her red blood cell count had shot up dramatically. The doctor was rubbing his hands together thinking that now they could re-start her on something like chemotherapy. She said something to the affect of "no thanks doc, I just wanted another opinion, adios." Since the hospital had essentially given her up for dead, she didn't want anything to do with them or with their killer medicines. With her renewed energy and new hope, she started seriously looking at alternative treatment options. She settled on a course of action and found a more sane approach to her condition south of the border in Mexico. 90 days later she was doing fantastic as her cancer was well in remission. What got her to turn the corner? An alternative health care practitioner with a microscope that understood the importance of key nutritional elements to the body. The body is such an incredible thing that if you work with it correctly, instead of against it, it is capable of tremendous self healing.

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**THE pH EQUATION & HEALTH** According to the research of Dr. Enderlein, total healing of chronic illness only takes place when and if the blood is restored to a normal, slightly alkaline pH. In case you missed it, let me say it again... **Total healing of chronic illness only takes place when and if the blood is restored to a normal, slightly alkaline pH.** The magnitude of meaning behind this research is of incredible importance to someone who is fighting a disease, overcoming an illness, or just desiring to feel better. What it means is this... **Your Body pH Affects EVERYTHING.** Human blood stays in a very narrow pH range right around 7.3. Below or above this range means symptoms and disease. When pH goes off, microorganisms in the blood can change shape, mutate, become pathogenic, and thrive. When pH goes off, ENZYMES that are constructive can become destructive. When pH goes off, OXYGEN delivery to cells suffer. A

**WORD ABOUT OXYGEN** *More and more research is showing that low oxygen delivery to cells is a major factor in most if not all degenerative conditions. Two time Nobel laureate, Dr. Otto Warburg of Germany, won his first Nobel Prize for his discovery of oxygen deficiency in the CANCER growth process. As stated above, when pH is off and our bodies are running more acid, our cells are getting less oxygen. Cancer thrives under an acid tissue pH/oxygen deficient environment. Is it any wonder today why cancer rates are up? To recall how important oxygen is to your life, just stop breathing for a minute. Get the idea? Each cell in your body can breathe fully or not. Which it is depends upon having an optimum pH balance. Do you think keeping an eye on your body pH might be important in your life?*

#### When pH goes off...

**MICROBES** in the blood can change shape, mutate, become pathogenic.

**ENZYMES** that are constructive can become destructive.

**OXYGEN** delivery to cells suffer.

**ORGANS** of the body can become compromised, like your brain, or your heart.

**MINERAL** assimilation can get thrown off.

**pH Controls the Things You Can't Live Without...** Like your BRAIN. Your brain needs fuel to run, and the fuel it uses is glucose. But unlike other cells, your brain can't store glucose. It depends on the second to second supply from the

bloodstream - a bloodstream that is affected by pH which controls the efficiency of INSULIN which allows sugar to enter into cells which in turn controls blood sugar levels. Your HEART. William Philpott M.D. in his 'Biomagnetic Handbook' made an important body pH/electrical connection. *As the pH of the blood goes more acid, fatty acids which are normally electro-magnetically charged on the negative side switch to positive and automatically are attracted to and begin to stick to the walls of arteries which are electro-magnetically charged on the negative side. (And as science states, opposites attract.) It should start to make sense that a society which over-emphasizes food that could push blood more acid will have a high rate of heart disease. And so it goes.* pH control impacts every biochemical process in our body including... ENZYMES which are part of that biochemical process. There are hundreds if not thousands of enzyme processes which take place in our body. Many are so specific that they are like complex square pegs that need to "fit" into specific square holes in order to carry out their duty. If blood pH is off balance even a little, some important pegs are not "fitting" their respective slots. Enzyme function and thus life itself begins to suffer. MINERAL ASSIMILATION is affected by pH.

Minerals have different pH levels at which they can be assimilated into the body. Minerals on the lower end of the atomic scale can be assimilated in a wider pH range, and minerals higher up on the scale require a narrower and narrower pH range in order to be assimilated by the body. For example.... Sodium and magnesium have wide pH assimilation ranges. It narrows somewhat for calcium and potassium. Narrows more for manganese and iron. More for zinc and copper. More for iodine. Iodine, which is high up on the atomic scale, requires near perfect pH for its assimilation into the body. Iodine you may know, is one of the most important minerals for proper functioning of the THYROID. But, the thyroid doesn't get access to iodine unless the body pH is near perfect. With a society in a largely pH unbalanced state, one would suspect a lot of thyroid problems. Malfunctioning thyroids have been connected to arthritis, heart attacks, diabetes, cancer, depression, overweight, fatigue and more. Are you starting to see the basic metabolic picture evolving here? Due primarily to agricultural soil depletion and over-acidic food consumption, mineral deficiency is a large problem facing most people today. And mineral deficiency relates to the quantity of life energy or more specifically, electricity in our bodies. **Body mineral content and balances control the quantity of electricity in our bodies.**

**The speed at which the electricity flows is controlled by its pH balance.**

**pH Balance and the Mineral Connection** There are complex biochemical processes taking place in the body constantly which attempt to keep blood pH as near perfect as possible. These are known as the pH buffering systems. These buffering systems need a good balance of minerals to work effectively. If we are getting inadequate mineral intake from the food we eat, we are going to start having problems with our pH balancing systems. And if our pH is unbalanced, what is the result? Well, by now you should start having a good idea. Pick your disease, choose your imbalance. Cancer, arthritis, diabetes, heart disease, chronic fatigue, allergies, obesity, just name it. If you don't feel good, one of the basic things that stand between you and perfect health is your bodies pH. Your basic metabolic body balance. **While We're on the Subject of Minerals.... Did**

you know that.... Minerals are as important, if not more important than vitamins. Minerals are co-enzymes which help vitamins function. In the absence of minerals, vitamins can't do their job. Many minerals are referred to as trace minerals, which might make it seem as though they are of little importance, but nothing could be further from the truth. Minerals and their deficiencies have been implicated in a wide range of off-balance health conditions. Here's some examples: Supplementing a diet with sufficient chromium and vanadium can help prevent diabetes and has been seen to reverse diabetes in those already diabetic as vanadium is reported able to replace insulin in some cases. Copper deficiency is implicated in aneurysms (brain, aortic, etc.) Magnesium is quite possibly the most important mineral for the reduction of coronary heart disease. (The latest "cutting edge" research shows that heart disease is really a function of heart muscle acidosis.) Boron helps keep calcium in the bones, helps women preserve and make estrogen, helps men keep testosterone. Boron affects alertness. Boron can help eliminate arthritis. Potassium and magnesium (along with organic sodium) are some of the most important minerals for rebalancing the electrical properties of the cell and eliminating excess acidity and help to balance calcium. Magnesium helps conduct electrical messages between all the neurons of the body. People get irrational when potassium levels are low. Zinc is involved in over 200 brain enzyme interactions. Drinking zinc mixed with distilled water can stop anorexia nervosa in a day. Zinc deficiency symptoms are loss of taste and smell. Zinc deficiency in children results in moodiness, depression, irritability, photo phobia (light sensitivity), antagonism, temper tantrums & learning problems. Children who do poorly on achievement tests tend to have low iron levels. These children also display disruptive, impulsive and irritable behavior in the classroom. Children who have high lead levels do more poorly overall. Most of these children's mineral imbalances go undiagnosed and instead are medicated with drugs. Likewise, ADD - Attention Deficit Disorder can often be eliminated by balancing nutritional trace minerals. There is no need to drug our children. Cigarette smoke is rich in cadmium (the blue color in the smoke). Cadmium is the most neurotoxic substance known to human beings. Low zinc/high cadmium ratios is implicated in learning disabilities. Zinc is needed to balance cadmium. Too much copper is an irritant to the brain. *A story is told by Dr. Alex Schauss, a noted author, researcher and nutritional mineral expert. It is about his experience with a 9 year old boy brought into his clinic some years ago. The boy was charged with attempted murder. His criminal record began at age 6. He burned animals, shot at peoples houses, beat up mothers pushing baby strollers. The police all said he will be a lifetime criminal, a Charles Manson type of psychotic. He was on six psychiatric drugs, and was kicked out of school after he tried to kill a 10 year old girl. Dr. Schauss did a hair mineral analysis and discovered his copper levels were off the charts. He added supplemental zinc to the boys diet to chelate out the excess copper, and within two weeks, the boys urinalysis showed all the excess copper had been eliminated. He went off all medication, returned to school and became a model student. Years later the boy returned to see Dr. Schauss. He*

before

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# CE MENS FUR PAIN

IT IS A SCIENTIFIC FACT THAT A LOW LEVEL VOLTAMMETRIC PULSE CAN INHIBIT PAIN SIGNALS.

THE SCIO WILL LET THE PATIENT'S BODY ELECTRIC AUTOFOCUS A HARMONIC PULSE TO MAXIMIZE THIS EFFECT. THIS IS CALLED

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was a junior in college, an A student, on the varsity basketball team and had a heart of gold. High manganese levels show statistically high correlation with violent behavior., while lithium balances and helps control manganese. The cities of the world with the highest lithium concentration in their water show the lowest homicide rates. The trace element rubidium cures manic depression. The right ratio of copper and zinc in the cell act as an antioxidant. This information shows just a teeny fraction of how minerals and their imbalances can affect your health. Much of it is found buried in professional journals, there for the taking. It appears that due to politics and the influence and strength that the medical/drug industrial complex has over the suppression of information, these things stay buried. If this type of information along with the other things we know could be assimilated into our society, whether through the efforts of individuals or that of our government, and if people like doctors, psychiatrists and dietitians were to act on it, we could lessen violence in our society, close jails, raise academic achievement, greatly reduce outlays of public money for Medicare and Medicaid, we could see our health insurance premiums drop to about \$50 dollars a month for a family of four because we could eliminate our need for expensive hospital visits and treatments excepting emergency care for accidents. Without a doubt, the single most important thing you can do for your health is to supplement your diet with broad spectrum trace minerals. They are that important. **Your Disease is in Perfect Harmony With Your Body** From what you've learned so far, you should begin to understand the truth to this statement. When your body mineral balances are off, your health is off. When your body pH and basic metabolic processes are off, it sets up the internal environment that becomes a new playground for the opportunistic "bugs"; bacteria, viruses, fungus, etc. Earlier we talked of the colloids of life in your blood (i.e. protits). How they form and what they evolve into is a function of pH - the terrain of the blood. What else is a constituent of the blood? How about the mineral balances we've been speaking about. Research has shown that the microbes of the blood can evolve into different forms when exposed and combined with elements like heavy metals. For example, patients with high levels of mercury in their mouths often exhibit specific pleomorphic microbes in their blood. Is it possible that something like high levels of copper as referenced in the story above, isn't just an irritant to the brain, but it sets up the internal environment in the body where the colloids of life form into specific "bugs" that with some level of microbial consciousness, actually is behind aggressive, violent or psychotic behavior? Some researchers would say that is exactly correct. And in so saying, your blood becomes much more than what you think it is.

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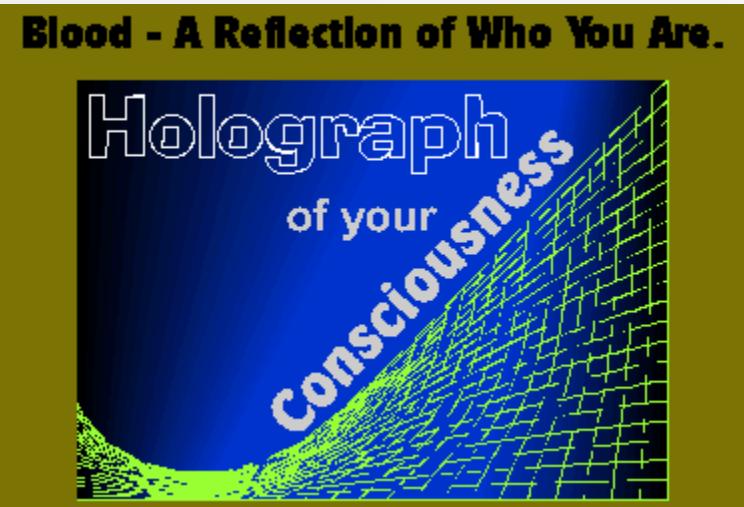
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### **How You Rot & Rust**



Peering into the microscope looking at live blood, we see cause and effect.

When you're not feeling well, your blood doesn't look good. Often, the worse you feel, the worse it looks. When you get better, the blood also gets to looking better. Simple correlation. Make the blood look better, you'll feel better. Clean the blood, clean your health. But something else is going on. When you feel better, often your attitude is also better. Your state of mental health is closely aligned with your state of physical health. Change physical health, and you'll often impact mental health. The reverse also holds, change the mental, and you'll change the physical. Where is it often reflected? In the blood. *Change your blood, and you'll change your consciousness. Change your consciousness, and you'll change your blood.* Our blood holds elements, or the vibrational imprint of who we are. It contains the signature of our soul. As the bible says, "The Life is in the Blood". Stories abound that correlate these truths. I recall someone asking at a seminar if anyone had ever had a blood transfusion and then feeling different afterwards. One gentleman said he had had a few transfusions and he definitely knew it when he had received his sister's blood because while in the hospital he had the urge to get up and start cleaning. He also knew it when he got his brother-in-law's blood because all he felt like doing was sitting around and watching TV. A humorous story maybe, but it holds some truth. In Australia, stories are told of the aboriginal people donating blood as urban life encroaches upon their existence. When normal white folk would get this blood during a transfusion, some have been known to wake up in the middle of the night sweating and grabbing the sides of their bed as they experienced night dreams beyond any like they've ever had before. Why? Blood holds the vibrational imprint of who we are. Similar stories are told of individuals who have had organ transplants. Having never liked certain foods, or doing certain things, or being proficient at specific tasks, they would suddenly find themselves after the transplant with cravings for food they hate and abilities they never before possessed. Why? The tissues of the body are fed by blood, which contains the vibrational imprint of who we are. Get someone else's blood or other organ tissue, and you have to assimilate their imprint and remake it your own. Like a giant human organic tape recorder, over time you erase their message with your own. When people have problems with transfusions and organ transplants, part of the problem lies in the vibrational makeup of both the donor and donee. In time, modern medicine may get around to understanding this, and they will discover how to electromagnetically and/or in other ways erase the donors imprint on blood and organ tissue. Along that time maybe they'll also understand more about the microbes in the blood and how blood needs to be assessed and treated at our blood banks. As you get deeper into this work and research its topics, a new way of looking at health will undoubtedly begin to unfold for you. Along the way, as you hear anecdotal stories of seemingly miracle cures using these ideas, you may begin to think of the placebo effect. Scientists have studied the power of the placebo and have seen explicitly that... ***you can make it so, if you think it so.*** And what has been said of thoughts? Thoughts are things, thoughts have power. You are what

you think. And what is a thought? It's a vibration of your mental self, behind which lies, who you really are; soul. And that is where the state of your health really begins. And it pushes down from there. It is a process that unfolds very simply, very beautifully. ***The State of Your Individual Health is***

***Spiritually/Vibrationally Induced, Chemically/Electrically Driven, &***

***Biologically Carried Out.*** The biological aspect is the pleomorphic behavior of "the wiggly things" in the blood. These are the microbial elemental forms that exist in your blood and will shape themselves according to your metabolic balance. Their forms, and ultimately their function, are going to be driven and decided by the environment in which they live, and to which you have provided through your eating, thinking, and living. *Whatever your current metabolic condition, the internal microbes or "bugs" will co-exist with you and will be in perfect balance (for them) whatever the environment you provide. Unfortunately, that can be very UNbalancing for you. To get healthy, you must balance your internal environment, and UNbalance the bugs.*

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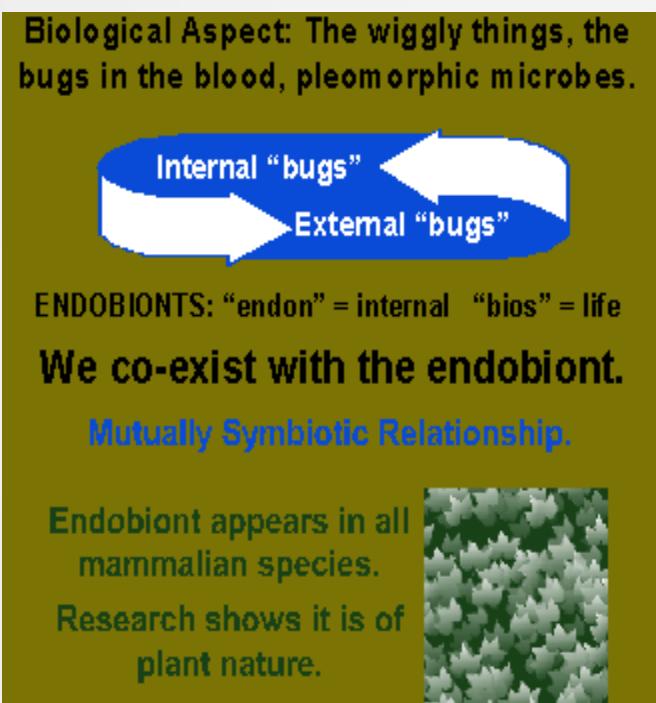
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## **How You Rot & Rust**

### **Differentiation Between the Internal and External "Parasites"**

**External "Parasites"** The colloids of life in your blood (i.e. protits) develop according to the terrain of the blood. At some stages of their development they are outright pathogenic and parasitic. They constitute the true fungus among us. These are our internal parasites. Professor Enderlein called these parasites ENDOBIONTS (from the Greek "endon" = internal and "bios" = life). We can never separate ourselves from them. We co-exist in a mutually symbiotic relationship. We give them a vehicle for life, they give us blood forms like platelets, without which we couldn't exist. The endobiont appears in all mammalian species and has shown evidence through some of its developmental forms to be of a plant nature. Our symbiotic union with them evidently occurred millions of years ago as our species grew into existence. Without some blood clotting mechanism in place, mammals could have never evolved. From my own perspective, this in no way counters the idea of creationism as God simply created this incredible plan with astounding brilliance. It even throws a new wrinkle on the story of Adam and Eve. When Adam (the beginning of man) first partook of the apple (plant), his form on earth was forever altered and he would hence experience physical death. The internal parasite (which actually looks like a snake or serpent in the blood when you're dying) would one day see to it. Now you can draw your own inferences however they suit you. The most important thing is that the internal parasite, the endobiont, is a concrete, indisputable and absolute element of human anatomy and physiology. It just happens to be unknown (or ignored) by traditional western medicine. **The External Parasites** The internal parasite which exists in us always, is in contrast to external parasites to which we occasionally come in contact. This is where the germ theory actually holds relevance. This is the area of external microbes and parasites that when taken to extremes, intensifies into infectious diseases and epidemics.

Surprisingly, without having even the slightest idea of pleomorphic biology, medicine through hygiene, has accomplished much in this area. The fact is, opportunistic bugs, bacteria and viruses are all over the place, including inside you, me, and others. Some of us get sick and some of us don't. As far back as the plagues of the dark ages some lived and some died. Nobody knew why. Could it be that pH balance, mineral balance, nutritional balance, all have something to do with which bugs thrive inside us and which don't? Absolutely. Disease producing organisms love off balance metabolic conditions. It's just like Pasteur had finally admitted, but nobody was around to hear. Until somebody listens and metabolic balancing catches on, the "experts" will be left confused and scratching their heads wondering why some people exposed to certain bacteria and viruses get sick and die, and some don't.



## How You Rot & Rust

**pH, BUGS, & ROT. Understanding Biological Terrain** When your body's blood pH changes away from the ideal, it can become an environment for opportunistic microorganisms to grow and flourish. **"Bugs in the blood" tell us the story of how we age, and how we ROT.** That's right, as we age, we rot. It is part of the disease process. It is the *biological aspect* of aging and disease. It is this rotting mechanism that helps to do us in and turn us back into the dust from which we came. There is a pH biochemical process which lies behind this rotting mechanism which I'll discuss in a moment. But you should also be aware as we talk that this is not the whole story on aging and disease, for there is also

an electrical/oxidative aspect. This is how we RUST. On the physical level, the aging and disease process is one of ROTTING AND RUSTING. Right now I'm going to talk about the rot, and I'll discuss the rust later. **The Biochemical Processes Behind pH Levels in Your Body.** Let me talk very simplistically about the biochemical processes which lay the groundwork for the rotting processes in your body. This is the process of pH change and alteration down at the blood and tissue level. In order to do this in a simple fashion, let's look at the process of food metabolism and how your body handles metabolic by-products from food intake. One of the by-products of food metabolism is CO<sub>2</sub>, carbon dioxide. As you know, lung respiration is one way in which your body eliminates carbon dioxide - it happens every time you exhale. However, in order to eliminate all of the carbon dioxide that is generated from normal metabolism, the lungs would need a respiration rate far above normal breathing. Holding this constantly accelerated rate would indeed be very difficult. Therefore, other mechanisms come into play for handling the excess. 1) The CO<sub>2</sub> combines with ammonia (produced from the oxidation of glutamine) and converts to urea in the liver and is excreted by the kidney. mineral ZINC. Through this process, carbonic acid is formed which breaks down into hydrogen and bicarbonate atoms/molecules. Aha - notice we just mentioned hydrogen. What does pH stand for??? Potential Hydrogen. When we talk about hydrogen, we are talking about potential ACIDS. When we talk of bicarbs, we are talking bases (alkaline substances). ACIDS are a normal by-product of metabolism. The body has the mechanisms in place to eliminate these acids. BUT, through poor dietary habits, shallow breathing, lack of exercise, toxicity exposures, etc., which can lead to liver stress and kidney malfunction, the ACIDS in the body do not always get eliminated as they should. In this case, what's a body to do? Well if it can't eliminate them, then it has to store them. And store them it does. When the body has an excess of acid it can't get rid of, it gets stored for later removal. Where? In the interstitial spaces, also called the extracellular matrix - the spaces around the cells; the mesenchyme. When the body stores a hydrogen molecule/atom/proton (the acid) in the extracellular matrix, it believes that one day, the acid is going to be removed. Therefore, in order to be in balance, it knows that for every molecule of acid that gets stored in the tissues, an equal molecule of bicarb or base needs to be put into the blood because one day it will need to escort the acid out of the body. This is the body's amazing compensatory mechanism at work. What we see here is the pH interplay between the blood and the tissues. If the body has an acid overload, it stores the acid in the tissues (the tissue pH decreases) and the blood compensates and becomes alkaline (the blood pH increases). Is this important? You bet it is. We are starting to scratch the surface for the rotting mechanism in our body. But before we get there, let's push on and see what happens when the acids don't get an opportunity to leave and more acid accumulates. **The Acidic/Mineral Bugaboo**

2)The carbon dioxide combines with water through a process utilizing the enzyme carbonic anhydrase and the co-enzyme mineral ZINC. Through this process, carbonic acid is formed which breaks down into hydrogen and

bicarbonate atoms/molecules.

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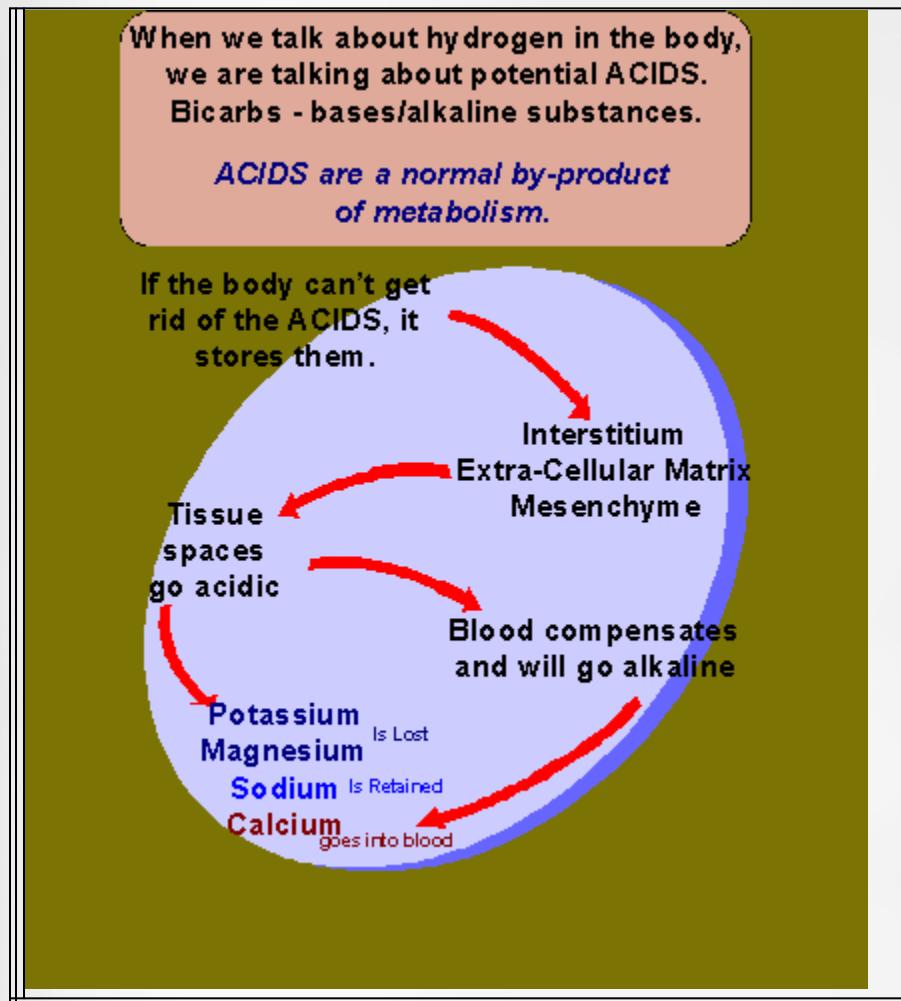
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### The Acidic/Mineral Bugaboo

#### The Acidic/Mineral Bugaboo



As more acid accumulates in our body, it gets stored and pushed further, and ultimately it gets pushed into the cell. When it gets pushed into the cell, the first thing it does is displace POTASSIUM and then MAGNESIUM and then SODIUM. Wow. Those are three critical minerals in our body. The potassium and magnesium will leave the body, but as a preservation mechanism the sodium will be retained. Remember, the body knows it must place an alkaline molecule in the blood to escort out this increasing acid that is being stored in the tissues and cells. What it will often do (when mineral reserves are low which is often the case when eating a modern american diet) is draw CALCIUM (the most alkaline mineral known) from the bones and put it into the blood. This leads to something called free calcium excess. This is something you don't want and it is what's behind osteoporosis, arthritic pain, etc. It is brought about by the body compensating for an ever increasing tissue acidosis somewhere in the body. What you don't want to do in this case is take more calcium supplements. With that said, you can now understand why calcium is one of the most over-prescribed supplements. In these situations what the body really needs is more potassium, and magnesium, perhaps organic sodium, and possibly zinc which lends help to the whole proper acid breakdown process which we started five paragraphs ago. Let's push a little further. We have discussed four critical minerals: - CALCIUM - MAGNESIUM - POTASSIUM - SODIUM Well, wouldn't you know, these four minerals are the controlling minerals for our body's

sympathetic and parasympathetic nervous system. Simply put, the sympathetic nervous system (SNS) controls our fight or flight response mechanism. The parasympathetic system (PSNS) controls our rest and digest response mechanism. It works like this: CALCIUM Stimulatory mineral for the Sympathetic Nervous System MAGNESIUM Inhibitory mineral for the Sympathetic Nervous System POTASSIUM Stimulatory mineral for the Parasympathetic Nervous System SODIUM Inhibitory mineral for the Parasympathetic Nervous System When you run an acidic condition in the body, free calcium is in excess which stimulates the SNS, magnesium isn't around to offer a balance; potassium is depleted so the PSNS is not getting stimulated to offset the SNS and it is actually being further inhibited by sodium which the body is hanging onto with respect to the loss of potassium and magnesium. What does this give you? A person that is acidic, possibly prone to ranting and raving, hyperactive, quick to anger, moving too fast, burning out. Just what you'd expect from somebody running too acidic. And pushed to the extreme? You get a person that may appear as extreme PSNS dominant, i.e. lazy, lethargic, fatigued, but what you usually have is a person pushed beyond SNS dominance to outright exhaustion. According to some health care practitioners, it is rare to see a true PSNS dominant individual. Metabolic reality, compensatory mechanisms, and today's modern diet rarely allows for PSNS dominance. What we've just covered is a bit of the biochemistry that gets us to where we're going, and as you can see, it's one of the many fascinating inter-related pieces to this puzzle we call health. Now let's go further to build the picture. **Acid/Base - Tissue/Blood - Biochemistry**

As acids accumulate in our body, they get stored and pushed into the tissues. Where they get pushed, on a local level, is going to be in large measure where in your body or with what organ you experience problems. When the body stores this excess acid, it will compensate and place an alkaline atom/molecule in the blood, and the blood will therefore become increasingly alkaline. Something interesting happens with the uptake of oxygen in blood with an overly alkaline environment. With rising alkalinity, blood can increase its oxygen uptake, therefore the blood cells can hold more oxygen. Pretty good don't you think? Well, if you think so, your wrong. The reason is, a little bit of biochemical reality known as the Bohr effect. The Bohr effect states that with rising blood alkalinity, the red blood cells can saturate themselves with ever more oxygen. The problem is, they can't let go of it! If the blood cells can't let go of oxygen, then the oxygen isn't getting down to the other cells of the body. And do you recall what Otto Warburg discovered about cancer? It grows in an oxygen deficient environment. Now let's go further. We have alkaline blood due to the fact we have increasingly acidic tissue and/or cells occurring somewhere in our body. We have an alkaline blood which can't let go of its oxygen to aerate an increasingly acidic environment. So get this ---- Here we have an Acidic environment with no oxygen. How can anything survive in this environment? Through anaerobic fermentation. What ferments anaerobically (i.e. without oxygen)? Yeast, mold and fungus. If that's the case, then this should bring up a most logical question; Since cancer thrives in an anaerobic environment, what is cancer? If you answered fermenting mold and fungus, you get a gold star. That is

exactly what cancer is. Want proof? In 1903, Enderlein and Schmitt (Munich) cultured the fungus *Mucor Racemosus Fresen* from tumor cells. Other biologists (some of those mentioned earlier) have done the same. With access to a biology lab, you or any other scientist not beholden to political agendas can duplicate this experiment at any time. Why is this important? Because it is part of the story behind the aging, disease, and the rotting process which confirms what pleomorphic scientists have known all along about MICROBES, i.e. ALL microbes will change dependent upon their environment.

**When you age, get cancer, experience diseases, part of the process is that...**

**YOU ARE ROTTING ON THE INSIDE**

It is a biological process pushed into action through biochemical principles.

### **Evolution of Microbes**

Microbes begin their life as a colloid - a near spec of almost nothingness - light into life - Anton Leuwenhoek's first experiment.

As microbe evolves, it will go through various bacterial stages, even viral.

Ultimately it will see a fungal (or yeast) culmination.

This is pleomorphism which all microbes will exhibit given time and a conducive terrain

This includes in the blood, where microbes exist in abundance. It is part of the ROT mechanism inherent in all mammals.

When you age, get cancer, experience diseases, part of the process is that YOU ARE ROTTING ON THE INSIDE. This is a biological anaerobic fermentative process pushed into operation through the biochemical principles explained here. Most of these principles have been taught in one way or another to every medical student alive today. They just weren't shown how it works in practice. (By golly if they were shown that, with a little cognitive brain power they could figure out how to cure cancer. And that definitely is not good for the natural order of political academic hierarchy or long term industrial health care profits.) That as it is, let's talk about the ROT. And the rot, as it biologically culminates in the human body, begins with the microbe that at its beginning stages we have identified as the protit. **Evolution of Microbes** Before we look at the life cycle of

the microbes in the blood, let's look at the evolution of microbes in general. I've already explained how a microbe begins its life as a colloid; a near spec of almost nothingness. Light into life. This will then evolve into a visible microbial particle that can be seen under the microscope (Anton Leuwenhoek's first experiment). These colloids are the building blocks of life. How they evolve is specifically a function of the terrain, the environment, or the medium in which they live or are cultured. As a microbe evolves, if you change its terrain or cultured environment, you'll see it going through various bacterial stages; i.e. round forms, rod shaped forms, even going into viral forms. Ultimately though, ALL microbes will see a FUNGAL CULMINATION. This fungal culmination can also be replaced by a YEAST CULMINATION. Biologists see microbes changing in the laboratory often, but for the most part dismiss it as contamination of their medium. The textbooks they learned from all held Pasteur's static ideas of "germs", and if something observed falls outside the standard textbook ideology, it is more often than not dismissed as laboratory contamination or aberration. Truth be told, it's usually the pleomorphic behavior that ALL microbial forms will exhibit if they are observed long enough and under the properly varying conditions. Which brings us to the blood. **Microbes exist in the blood.** If the blood terrain changes (i.e. pH etc.), the microbes will change their shape - bacterial - viral - yeast - fungus. Yep. There is a fungus among us, and it's in our blood and we get ROT. Part of the biological aging and disease process. This is why if you take a cancer tumor and culture it, you will get the fungus mucor racemosus fresen. Why that particular fungus? Because that is the species of plant based fungus that Professor Guenther Enderlein discovered has infected man and all mammalian species millennia ago! This is the Endobiont, the internal parasitic life with which we live. If health care biologists want a new road to explore for finding "cures" to today's diseases, all they need to do is adopt pleomorphic thinking and dig into Professor Enderlein's research.

Give it the proper terrain (or more to the point improper terrain) and we get ROT. Part of the biological aging and disease process.

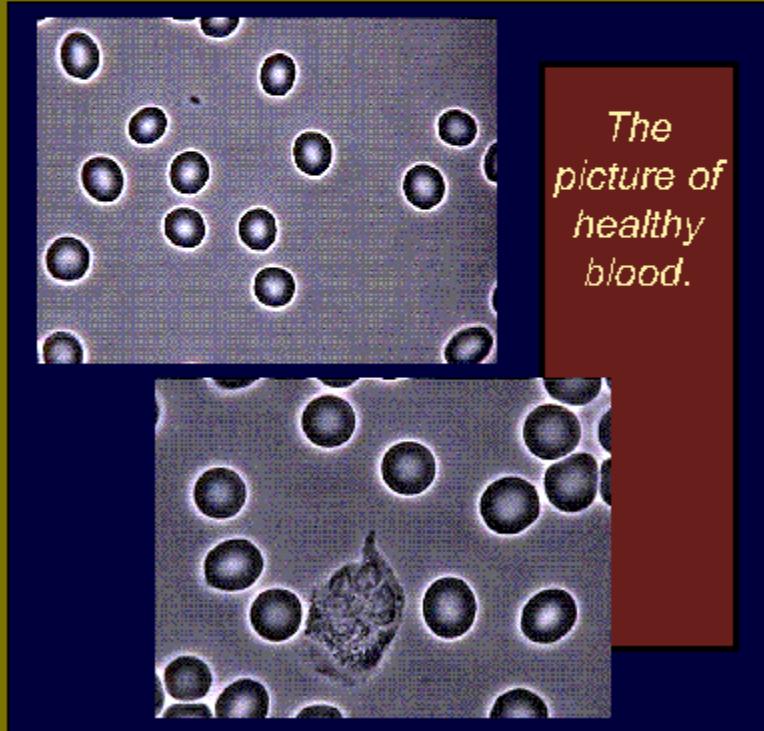
This is why if you take a cancer tumor and culture it, you will get the fungus mucor racemosus fresen. Why that particular fungus? Because that is the species of plant based fungus that Professor Guenther Enderlein discovered has infected man and all mammalian species millennia ago! This is the Endobiont, the internal parasitic life with which we live. If health care biologists want a new road to explore for finding "cures" to today's diseases, all they need to do is adopt pleomorphic thinking and dig into Professor Enderlein's research.

#### How You Rot & Rust

## A Visual Look at How We Rot

The microscope is a tool to learn about the ROT theory of aging and disease.

*The faster live blood degenerates on a microscope slide, the faster the patient is aging and degenerating internally.*

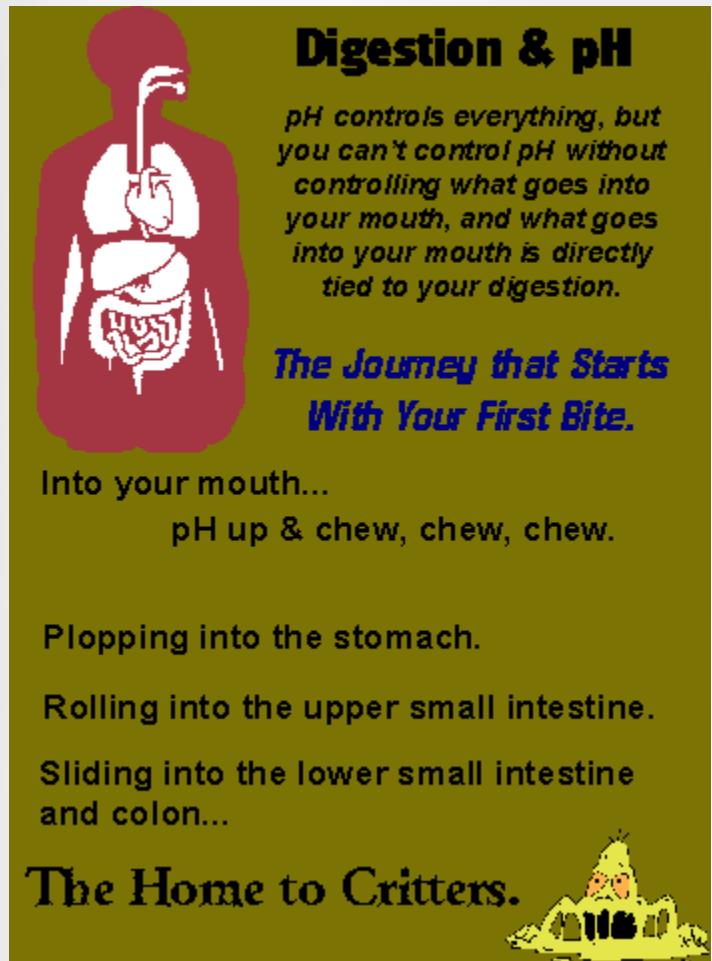


**Pictures of Blood - A Visual Look at How We Rot** Using a microscope in a health care practice becomes a most powerful tool to visually see the microbial activity in blood and learn firsthand about the ROT theory of aging and disease. To say it impacts patients is an understatement. When a patient visually sees the microbial activity taking place in their own blood, it gives them reason to pause and rethink their health attitudes - unless of course they don't care about their health. But if they do care, it makes a lasting and positive impact on patients like few other things. Looking at live blood under the microscope, with an understanding of what is going on, is an education in health beyond what words can impart. The blood that used for observation under the microscope is simple capillary blood, expelled from the pinky through a simple finger stick. In order to not damage the blood, the finger is not squeezed, the blood is allowed to come out on its own and it is quickly placed on a slide with a cover slip. Blood should be observed immediately after getting the specimen. The reason we do this is because it immediately tells us something - and that is; where is the patient "right now". You see, as blood sits on a slide, it degenerates. HOW FAST it degenerates when out of the body, tells us HOW FAST the patient themselves

are AGING and DEGENERATING. *The faster live blood degenerates on a microscope slide, the faster the patient is aging and degenerating internally.*

The preceding pages covered some key concepts relative to the rotting mechanism of the body. The rotting mechanism of the body is the biological equation. The flip side to this is the rusting mechanism, which is a chemical and electrical equation. As we age and get diseases, we are experiencing the effects of Rot & Rust. It is an interplay of the biological, chemical, and electrical physiology of the human body. With a firm understanding of this knowledge, the microscope becomes a tool to delve into this interplay at its most basic level - in the blood. This whole section has been a peek into our microscope pre-training program that lays the foundation for the advanced work. We've discussed pH and introduced biological terrain, and in our workshops we take it much further, incorporating things like redox (reduction/oxidation) and the principles of rust. We also get into detail on a few other items, all in an effort to solidly understand biological terrain and its influence on the live blood and dry layer analysis. To give you a little more flavor for this workshop, some additional transparency out-takes follow along with brief commentary on a few of them.

# Hematopathology



**Digestion & pH**

*pH controls everything, but you can't control pH without controlling what goes into your mouth, and what goes into your mouth is directly tied to your digestion.*

**The Journey that Starts With Your First Bite.**

Into your mouth...  
pH up & chew, chew, chew.

Plopping into the stomach.

Rolling into the upper small intestine.

Sliding into the lower small intestine and colon...

**The Home to Critters.**

**Home of the “Critters”**

**Bacteria**

Probiotic - For Life  
Antibiotic - Against Life

Probiotic Bacteria support life processes

Primary Probiotic bacteria of lower small intestine is Lactobacillus Acidophilus. Of the colon, Bifidobacterium Bifidum (bifidus)

**The Good Guys vs. The Bad Guys**

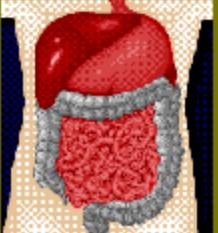
**TOXINS**

Guanadine  
Alloxan  
Methyl Colanthrene  
Candida (yeast)  
Acetaldehyde

**PARASITES**

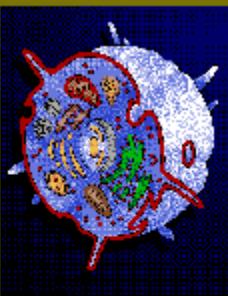
Underweight / Overweight

**Death Begins in the Colon**

## The Body's Cellular Energy Plant

*Every cell in your body has its' own energy factory. The furnace for that factory, or the generator that delivers the goods, is called the mitochondria.*



*The mitochondria is the power plant inside every cell in your body.*

**REDUCTION  
OXIDATION  
REDOX**

***The Chemistry  
of Life***

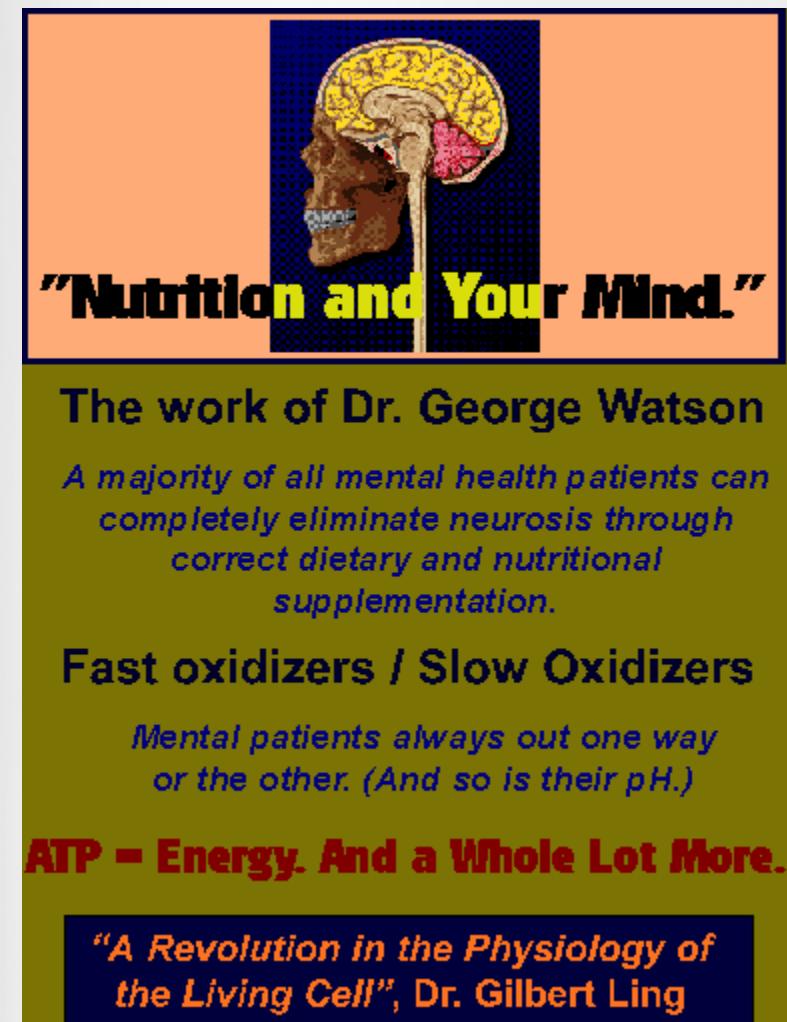
**THE FLOW OF LIFE MOVES WITH THE  
FLOW OF ELECTRONS.**

***Food into energy.***

Carbohydrates > glucose > delivered to cell >  
pyruvic acid (GLYCOLYSIS)

Pyruvic acid > acetyl CoA > mitochondria  
Krebs “spin cycle” > Electron Transport Chain

Haematology



## Electrons, Oxidation, & Rust

REDOX

*The  
Electron  
Shuffle*

ATP

**Burns up Toxins**  
Endotoxins  
Mycotoxins  
Exotoxins  
Xenotoxins

**Concept #1**

When atoms meet,  
they share electrons  
which make a "pair" -  
covalent bond.

If electron stripped off,  
it becomes unpaired -  
a *free radical*.  
A A A A A A A A

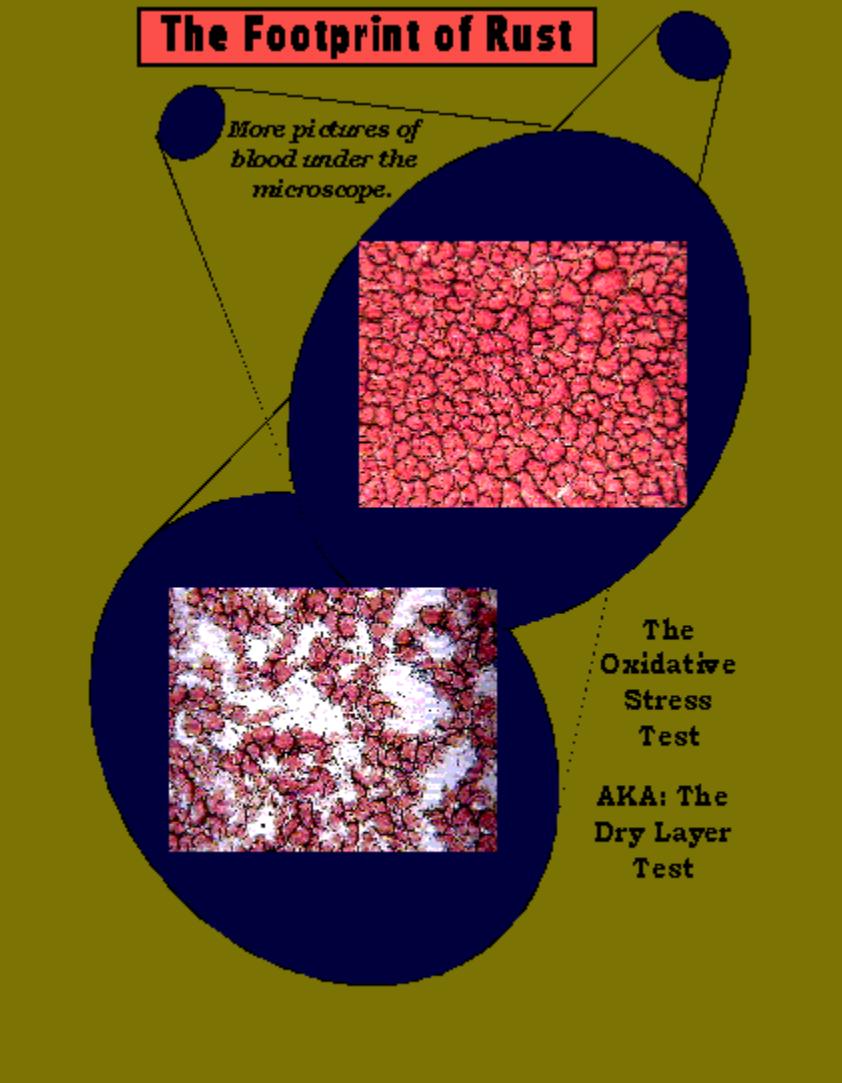
**Concept #2**

In life, things oxidize.  
Molecules give up  
electrons to oxygen.  
Molecules of metal.  
Molecules of the body.

As you age you  
rust. Or, as you  
rust, you age.

**Free Radicals / The Two Edged Sword.**

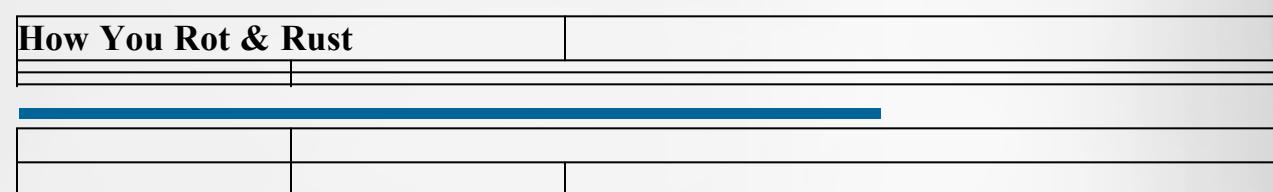
How You Rot & Rust



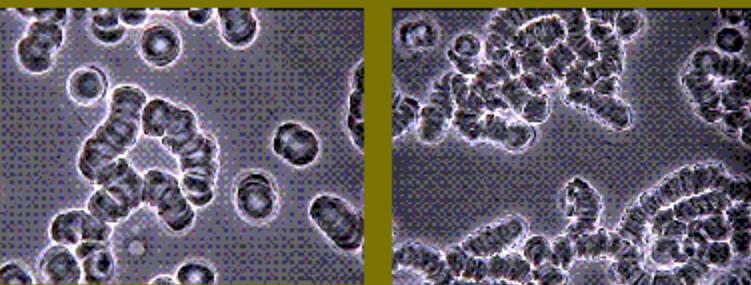
Healthcare  
Hematology

Health care practitioners that use a microscope in their practice for patient education have a unique ability to observe the extent of free radical activity taking place in the body. This is through a procedure called the Dry Layer Oxidative Stress Test. It is very simple. A drop of blood from the finger tip is placed on a specimen slide in a series of layers. After the layers dry, they are observed under the microscope. Blood is an interesting indicator of health and where free radicals are concerned, their activity impacts blood morphology. Putting it very simply, when free radicals attack cells, damage is done. The stuff that lies between cells and holds them together is the interstitium, or extra cellular matrix. Through free radical attack, cells get damaged, enzyme activity is altered, and the extra cellular matrix around the cells becomes compromised. Water soluble fragments of this matrix get into the blood stream and then alters the blood clotting cascade. With that done, we find that blood does not coagulate perfectly. This is one mechanism for altering a "normal" blood pattern. Reading the dry layers of blood is like reading an ink blot. It can be very revealing as to the overall state of one's health. Blood from a healthy person will be uniform in coagulation, and tightly connected. From an individual with health problems and excess free radical activity, the dry layer blood profile will be disconnected,

showing puddles of white (known as polymerized protein puddles). The more ill the patient with free radical/oxidative stress, the more disconnected is the dried layer of blood. The image on above on top is the blood of a healthy individual. Notice how it is inter-connected with black connecting lines. The black interconnecting lines is a fibrin network. This is fibrinogen, one of the protein constituents of the blood. In-between the fibrinogen are the red blood cells. The image on the bottom a cancer patient. Notice how the blood fails to coagulate completely and has many white areas. These are the polymerized protein puddles and they reflect oxidative stress. They represent the degradation of the body's extra cellular matrix from free radical activity. Since free radical activity has been implicated in nearly all disease processes, this test can be used as a quick reference to gauge the severity and extent of one's health problems.



**THE GENETIC CONNECTION**



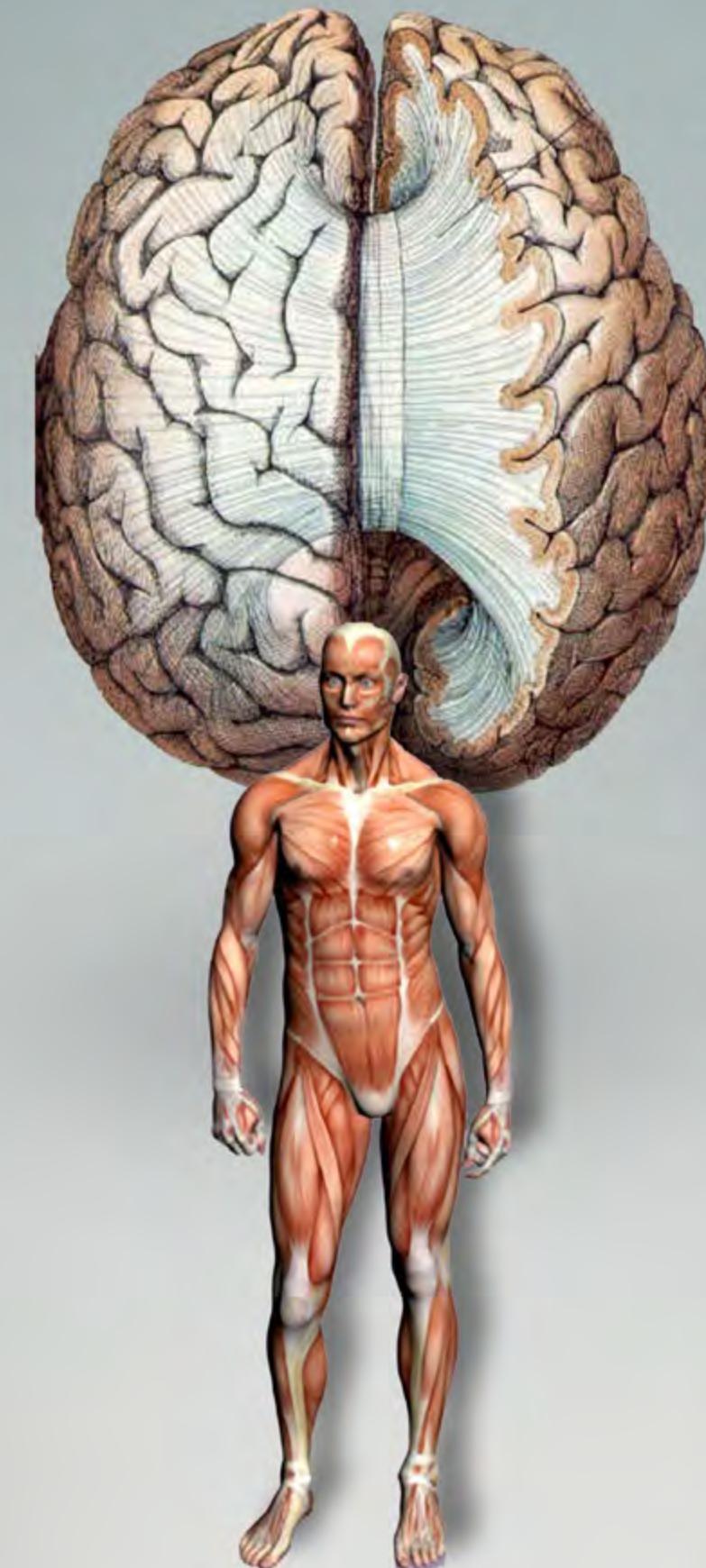
**Type**

O A B AB

Determines food compatibility or incompatibility. Food can act like medicine, food or poison.

**The Secret is Lectins / Agglutination**

Molecular Velcro™



# CE Corpus

*The Energy Band*

## Callosum

*Regulator of the Body*

The SCIO device can use the Trivector and Cybernetic Loop to rectify aberrant and disharmonious energy patterns in the body. This has profound effects on all body functions but affects the corpus callosum most intensely.

This means that the ability of the conscious verbal mind to relate to the subconscious is increased with the rectification process. The patient will probably not feel the effect. There will always be a positive effect. If there is a negative effect, it is because there is shielded or covert feelings or memories in the subconscious. These will cause disease if left untreated. A simple release may solve the problem.

**The changes include:**

1. Activate the innate intelligence to balance the body energies. This is the basic principle of chiropractic, acupuncture, and osteopathy medicine.
2. There is an easier exchange of energy and information from right brain to left brain via the corpus callosum. The corpus callosum is the largest energy form in the body and the rectification process has profound effects on stabilizing it, so it dramatically reduces switching phenomena.
3. The SCIO thereby increases the ability of the conscious to interface with the unconscious. This allows greater knowledge of self and of the higher self.
4. There is a greater memory access, a more true access of memory without emotional clouding.
5. There is a greater flexibility of connective tissue, allowing for more resilience.
6. There is a greater oxygenation and hydration ability of the body.
7. There is a smoother muscle control.
8. There is a general increase in well being that the conscious mind is so often unable to perceive. And thus there are thousands of subtle improvements to be found.

If you need more information on the SCIO and purchase details please get in touch with us

**Maitreya Kft.**

tel: +3613036043 | web: [www.qxsubspace.com](http://www.qxsubspace.com) | e-mail: [info@qxsubspace.com](mailto:info@qxsubspace.com)

## Can looking at blood under the microscope tell you

something about genetic predisposition? With reference to other things, in a way it can. The following two pictures highlight blood in which the red blood cells are sticking together (agglutinating). This is not a good situation for most people.

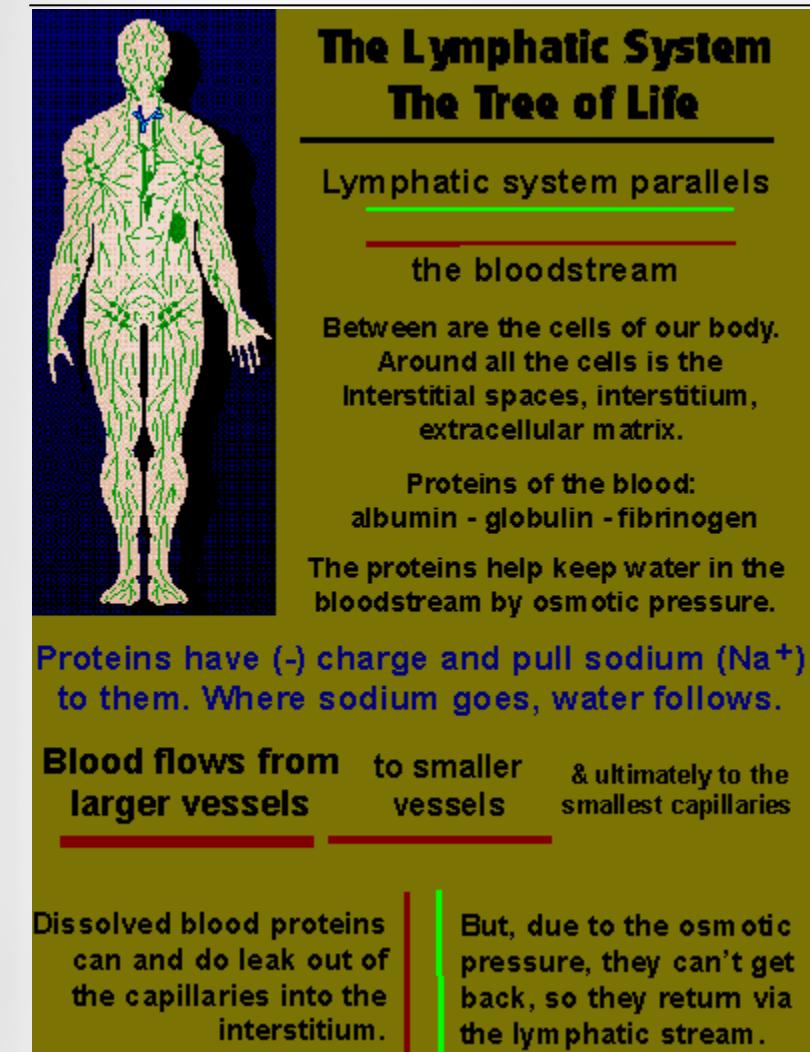
Red blood cells bring oxygen to every other cell in the body, and when they are stuck together like this, they are not doing their job as well as they should.

Generally, live blood microscopists have related this blood picture to having excess protein in the diet, or to the patient having a lack of adequate protein digestion. On one level this could be true, but it goes much further. More specifically, it begs the question, what "type" of protein has been in the patients diet most recently that has possibly caused this condition? Even more to the point, what type of protein or food group in relation to the patients specific blood type - as in O, A, B or AB. Certain foods, and food groups act like poisons to certain blood types. What can be a medicine for one person, can be a poison for another. How is this possible? Because of genetics. You were born with a basic blood type. O, A, B, or AB. You got it from your parents genes. Genes have a way of representing a bit of genetic history. Type O blood is the oldest blood and shows a connection to the hunter-gatherer cultures. This blood type is strongly aligned with high protein consumption in the form of animal meat and individuals with type O blood generally produces higher stomach acids. This is typically the group that experiences more incidence of gastric ulcer disease than the other groups. Type O's handle animal protein well but grains like whole wheat, and dairy products are not so good. Type O groups comprise about 46% of the American population. Blood group A was the next to evolve and merged with the development of agricultural practices. Blood group A is primarily associated with vegetarian food sources and individuals in that group secrete smaller amounts of stomach acid. Protein requirements are not any less than a group O person but the source is different. Type A's do poorly with the typical meat and potato fare and are predisposed to heart disease, cancer, and diabetes. Soy proteins, grains, and vegetables are very important for type A's as well as food that is fresh, pure and organic. Group A comprises 42% of the American population. There is type B and AB. The key to all of this is lectin chemistry. Different blood types are incompatible with the lectins (proteins) of certain food groups. In learning live blood microscopy, the clinician needs to intimately understand the importance of serotyping (blood typing) and the patient's dietary history in relationship to the microscopic findings.

Then there is type B and AB.

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## How You Rot & Rust



The lymphatic system is the body's second circulatory system and plays a crucial role in maintaining homeostasis and a centered biological terrain. Also, it exerts incredible influence on free radical pathology. There is an inseparable relationship between the blood stream and the lymphatics. The live blood/dry layer microscopist needs to fully understand these relationships as the dry layer analysis can highlight aberrant lymphatic function while giving indications to the anatomical area that may be dysfunctional.

## Inflammation A Review for Biofeedback Therapists

The local response to injury, involving small blood vessels, the cells circulating within these vessels, and nearby connective tissue.

The early phases of the inflammatory response are stereotyped: A similar sequence of events occurs in a variety of tissue sites in response to a diversity of injuries. The response characteristically begins with hyperemia, edema, and adherence of the circulating white blood cells to endothelial cells. The white cells then migrate between the endothelial cells of the blood vessel into the tissue. The subsequent development of the inflammatory process is determined by factors such as type and location of injury, immune state of the host, and the use of therapeutic agents. *See also* Circulation; Edema.

A local inflammatory response is usually accompanied by systemic changes: fever, malaise, an increase in circulating leukocytes (leukocytosis), and increases in specific circulating proteins called acute-phase reactants. Such signals and symptoms are often helpful to the physician, first as clues to the presence of **inflammation** and later as an indication of its course.

The process of **inflammation**, both vascular and cellular, is orchestrated by an array of molecules produced locally. These mediators include histamine, leukotrienes, prostaglandins, complement components, kinins, antibodies, and interleukins. Many anti-inflammatory drugs function by preventing the formation of those mediators or by blocking their actions on the target cells whose behavior is modified by the mediators.

**Inflammation** is basically a protective mechanism. The leakage of water and protein into the injured area brings humoral factors, including antibodies, into the locale and may serve to dilute soluble toxic substances and wash them away. The adherence and migration of leukocytes brings them to the local site to deal with infectious agents. There are also instances in which no causative toxic substance or infectious agent can be found to account for the **inflammation**. This is the case in rheumatoid arthritis and rheumatic fever. Such diseases may be examples in which an uncontrolled or misdirected inflammatory response with an autoimmune component is turned against the host. *See also* Arthritis; Autoimmunity; Infection; Rheumatic fever.

### **inflammation**

*noun*

An instance of being irritated, as in a part of the body: irritation, soreness.

*See* help/harm/harmless.

### Britannica Concise Encyclopedia

#### **inflammation**

Local reaction of living tissues to injury or illness, including burns, pneumonia, leprosy, tuberculosis, and rheumatoid arthritis. Its major signs are heat, redness, swelling, and pain. The process begins with brief contraction of nearby arterioles (*see* arteries). Dilation follows, flushing

the capillaries with blood, from which fluid, plasma proteins, and leukocytes pass into the injured tissues, causing swelling as they attack the cause of injury. Initial acute **inflammation** can have any of four outcomes: resolution (return to normal), organization (new tissue buildup; *see* scar), suppuration (pus formation; *see* abscess), or chronic **inflammation**. Sometimes treatment — including antibiotics for bacteria, or surgical removal of an irritating foreign body — can eliminate the cause. If not, anti-inflammatory drugs (e.g., cortisone or aspirin) may be given, or simple remedies (e.g., hot or cold compresses) may be applied.

*For more information on* inflammation, visit Britannica.com.

### Columbia Encyclopedia

**inflammation**, reaction of the body to injury or to infectious, allergic, or chemical irritation. The symptoms are redness, swelling, heat, and pain resulting from dilation of the blood vessels in the affected part with loss of plasma and leucocytes (white blood cells) into the tissues. White blood cells communicate with each other via cytokines, which are polypeptides released by cells of the immune system that regulate other cells. They are a broad class of soluble compounds that signal one cell type to another, particularly in response to foreign substances. Granulomas are most common in infectious diseases such as tuberculosis, leishmaniasis, and schistosomiasis, in which the body's defenses, unable to destroy the offending organisms, try to enclose them in a mass of inflammatory cells. Certain types of **inflammation** result in pus formation, as in an abscess. The leukocytes destroy harmful microorganisms and dead cells, preventing the spread of the irritation and permitting the injured tissue to repair itself.

### Veterinary Dictionary

#### **inflammation**

A localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue.

The inflammatory response can be provoked by physical, chemical and biological agents, including mechanical trauma, exposure to excessive amounts of sunlight, x-rays and radioactive materials, corrosive chemicals, extremes of heat and cold, and infectious agents such as bacteria, viruses and other pathogenic microorganisms. Although these infectious agents can produce **inflammation**, infection and **inflammation** are not synonymous.

The classic signs of **inflammation** are *heat, redness, swelling, pain and loss of function*. These are manifestations of the physiological changes that occur during the inflammatory process. The three major components of this process are: (1) changes in the caliber of blood vessels and the rate of blood flow through them (hemodynamic changes); (2) increased capillary permeability; and (3) leukocytic exudation.

- acute i. — **inflammation**, usually of sudden onset, marked by the classic signs of heat, redness, swelling, pain and loss of function, and in which vascular and exudative processes predominate.
- adhesive i. — promotes adhesion of adjacent surfaces.
- atrophic i. — one that causes atrophy and deformity.
- catarrhal i. — a form affecting mainly a mucous surface, marked by a copious discharge

of mucus and epithelial debris.

- chronic i. — prolonged and persistent **inflammation** marked chiefly by new connective tissue formation; it may be a continuation of an acute form or a prolonged low-grade form.
- chronic i. bowel disease of sheep — a syndrome of unknown etiology, manifest with wasting, ill thrift and mortality or culling for poor production. Reported in England and Canada, it affects both housed and pastured sheep, predominantly in their first year of life, but cases up to three years-of-age have been seen. Affected sheep are dull and anorectic with pale mucous membranes and have fecal staining of the perineum. The rumen fill is reduced and the feces are soft and malodorous. Blood examination shows hypoalbuminemia, an elevated blood urea nitrogen and leukocytosis with neutrophilia. On postmortem there is a lymphocytic enteritis with gross thickening of segments or the entire or distal part of the small intestine. There is no evidence for Johne's disease or parasitic gastroenteritis and the syndrome has similarities to the proliferative enteropathies of swine and horses.
- croupous i. — a homogeneous layer of exudate lying close to but detached from the underlying inflamed tissue, which is comparatively unharmed; may form a fibrinous cast.
- diphtheritic i. — manifested by the development of a fibrinous exudate which is firmly attached to the underlying tissue, such that it cannot be removed except by tearing off a superficial layer.
- exudative i. — one in which the prominent feature is an exudate.
- fibrinous i. — one marked by an exudate of coagulated fibrin.
- fibrous i. — leads to the development of fibrous tissue.
- granulomatous i. — a form, usually chronic, attended by formation of granulomas.
- hyperplastic i. — leads to the development of new connective tissue.
- hypertrophic i. — leading to the enlargement of the affected tissues.
- interstitial i. — **inflammation** affecting chiefly the stroma of an organ.
- obliterative i. — **inflammation** within a vessel or viscus leading to occlusion of the lumen.
- parenchymatous i. — **inflammation** affecting chiefly the essential tissue elements of an organ.
- productive i., proliferative i. — one leading to the production of new connective tissue fibers.
- pseudomembranous i. — an acute inflammatory response to a powerful necrotizing toxin, e.g. *Fusobacterium necrophorum* toxin, characterized by formation on a mucosal surface of a *false* membrane composed of precipitated fibrin, necrotic epithelium and

inflammatory leukocytes. See also diphtheritic **inflammation** (above).

- purulent i. — suppurative **inflammation**.
- serous i. — one producing a serous exudate.
- specific i. — one due to a particular microorganism.
- systemic i. response syndrome (SIRS) — a generalized inflammatory response with vasodilation of capillaries and postcapillary venules, increased permeability of capillaries, and hypovolemia. Depressed cardiac function and decreased organ perfusion follow. The various initiating stimuli include sepsis and septic shock, hyperthermia, pancreatitis, trauma, snake bite and immune-mediated diseases.
- toxic i. — one due to a poison, e.g. a bacterial product.
- traumatic i. — one that follows a wound or injury.
- ulcerative i. — that in which necrosis on or near the surface leads to loss of tissue and creation of a local defect or ulcer.



An abscess on the skin, showing the redness and swelling characteristic of **inflammation**. Black rings of necrotic tissue surround central areas of pus.

**Inflammation** (Latin, *inflammatio*, to set on fire) is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. **Inflammation** is not a synonym for infection. Even in cases where **inflammation** is caused by infection it is incorrect to use the terms as synonyms: infection is caused by an exogenous pathogen, while **inflammation** is the response of the organism to the pathogen.

In the absence of **inflammation**, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. However, **inflammation** which runs unchecked can also lead to a host of diseases, such as hay.

fever, atherosclerosis, and rheumatoid arthritis. It is for this reason that **inflammation** is normally tightly regulated by the body.

**Inflammation** can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged **inflammation**, known as *chronic inflammation*, leads to a progressive shift in the type of cells which are present at the site of **inflammation** and is characterised by simultaneous destruction and healing of the tissue from the inflammatory process.

## Causes

- Burns
- Chemical irritants
- Frostbite
- Toxins
- Infection by pathogens
- Necrosis
- Physical injury, blunt or penetrating
- Immune reactions due to hypersensitivity
- Ionizing radiation
- Foreign bodies, including splinters and dirt

## Types

### Comparison between acute and chronic **inflammation**:

	Acute	Chronic
<i>Causative agent</i>	Pathogens, injured tissues	Persistent acute <b>inflammation</b> due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
<i>Major cells involved</i>	Neutrophils	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
<i>Primary mediators</i>	Vasoactive amines, eicosanoids	IFN- $\gamma$ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
<i>Onset</i>	Immediate	Delayed
<i>Duration</i>	Few days	Up to many months, or years
<i>Outcomes</i>	Healing, abscess formation, chronic <b>inflammation</b>	Tissue destruction, fibrosis

### Acute inflammation

The classic signs and symptoms of acute **inflammation**:

English	Latin
Redness	<i>Rubor</i>
Heat	<i>Calor</i>
Swelling	<i>Tumor</i>
Pain	<i>Dolor</i>
Loss of function	<i>Functio laesa</i>



Infected ingrown toenail showing the characteristic redness and swelling associated with acute **inflammation**

Acute **inflammation** is a short-term process which is characterised by the classic signs of **inflammation** - swelling, redness, pain, heat, and loss of function - due to the infiltration of the tissues by plasma and leukocytes. It occurs as long as the injurious stimulus is present and ceases once the stimulus has been removed, broken down, or walled off by scarring (fibrosis). The first four characteristics have been known since ancient times and are attributed to Celsus. *Loss of function* was added to the definition of **inflammation** by Rudolf Virchow in the 19th century<sup>[1]</sup>.

The process of acute **inflammation** is initiated by the blood vessels local to the injured tissue, which alter to allow the exudation of plasma proteins and leukocytes into the surrounding tissue. The increased flow of fluid into the tissue causes the characteristic swelling associated with **inflammation**, and the increased blood flow to the area causes the reddened colour and increased heat. The blood vessels also alter to permit the extravasation of leukocytes through the endothelium and basement membrane constituting the blood vessel. Once in the tissue, the cells migrate along a chemotactic gradient to reach the site of injury, where they can attempt to remove the stimulus and repair the tissue.

Meanwhile, several biochemical cascade systems, consisting of chemicals known as plasma-derived inflammatory mediators, act in parallel to propagate and mature the inflammatory response. These include the complement system, coagulation system and fibrinolysis system.

Finally, down-regulation of the inflammatory response concludes acute **inflammation**. Removal of the injurious stimuli halts the response of the inflammatory mechanisms, which require constant stimulation to propagate the process. Additionally, many inflammatory mediators have short half lives and are quickly degraded in the tissue, helping to quickly cease the inflammatory response once the stimulus has been removed<sup>[1]</sup>.

### Chronic inflammation

*Main article: Chronic inflammation*

Chronic **inflammation** is a pathological condition characterised by concurrent active **inflammation**, tissue destruction, and attempts at repair. Chronic **inflammation** is not characterised by the classic signs of acute **inflammation** listed above. Instead, chronically inflamed tissue is characterised by the infiltration of mononuclear immune cells (monocytes, macrophages, lymphocytes, and plasma cells), tissue destruction, and attempts at

healing, which include angiogenesis and fibrosis.

Endogenous causes include persistent acute **inflammation**. Exogenous causes are varied and include bacterial infection, especially by Mycobacterium tuberculosis, prolonged exposure to chemical agents such as silica, or autoimmune reactions such as rheumatoid arthritis.

In acute **inflammation**, removal of the stimulus halts the recruitment of monocytes (which become macrophages under appropriate activation) into the inflamed tissue, and existing macrophages exit the tissue via lymphatics. However in chronically inflamed tissue the stimulus is persistent, and therefore recruitment of monocytes is maintained, existing macrophages are tethered in place, and proliferation of macrophages is stimulated (especially in atheromatous plaques).<sup>[1]</sup>

## Exudative component

The *exudative component* involves the movement of plasma fluid, containing important proteins such as fibrin and immunoglobulins (antibodies), into inflamed tissue. This movement is achieved via the chemically-induced dilation and increased permeability of blood vessels, which results in a net loss of blood plasma. The increased collection of fluid into the tissue causes it to swell (edema).

## Vascular changes

Acute **inflammation** is characterised by marked vascular changes, including vasodilation, increased permeability, and the slowing of blood flow, which are induced by the actions of various inflammatory mediators. Vasodilation occurs first at the arteriole level, progressing to the capillary level, and brings about a net increase in the amount of blood present, causing the redness and heat of **inflammation**. Increased permeability of the vessels results in the movement of plasma into the tissues, with resultant *stasis* due to the increase in the concentration of the cells within blood - a condition characterised by enlarged vessels packed with cells. Stasis allows leukocytes to marginate along the endothelium, a process critical to their recruitment into the tissues. Normal flowing blood prevents this, as the shearing force along the periphery of the vessels moves cells in the blood into the middle of the vessel.

## Plasma cascade systems

- The complement system, when activated, results in the increased removal of pathogens via opsonisation and phagocytosis.
- The kinin system generates proteins capable of sustaining vasodilation and other physical inflammatory effects.
- The coagulation system or *clotting cascade* which forms a protective protein mesh over sites of injury.
- The fibrinolysis system, which acts in opposition to the coagulation system, to counterbalance clotting and generate several other inflammatory mediators.

## Plasma derived mediators

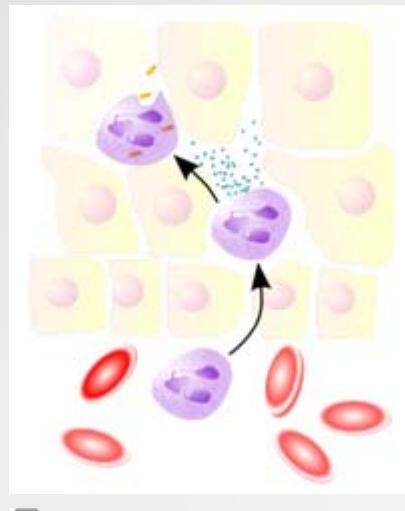
\* non-exhaustive list

Name	Produced by	Description
<u>Bradykinin</u>	<u>Kinin system</u>	A vasoactive protein which is able to induce vasodilation, increase vascular permeability, cause smooth muscle contraction, and induce pain.
<u>C3</u>	<u>Complement system</u>	Cleaves to produce <u>C3a</u> and <u>C3b</u> . C3a stimulates histamine release by mast cells, thereby producing vasodilation. C3b is able to bind to bacterial cell walls and act as an <u>opsonin</u> , which marks the invader as a target for <u>phagocytosis</u> .
<u>C5a</u>	<u>Complement system</u>	Stimulates histamine release by mast cells, thereby producing vasodilation. It is also able to act as a <u>chemoattractant</u> to direct cells via chemotaxis to the site of <b>inflammation</b> .
<u>Factor XII (Hageman Factor)</u>	<u>Liver</u>	A protein which circulates inactively, until activated by collagen, platelets, or exposed <u>basement membranes</u> via <u>conformational change</u> . When activated, it in turn is able to activate three plasma systems involved in <b>inflammation</b> : the kinin system, fibrinolysis system, and coagulation system.
<u>Membrane attack complex</u>	<u>Complement system</u>	A complex of the complement proteins <u>C5b</u> , <u>C6</u> , <u>C7</u> , <u>C8</u> , and multiple units of <u>C9</u> . The combination and activation of this range of complement proteins forms the <i>membrane attack complex</i> , which is able to insert into bacterial cell walls and causes cell lysis with ensuing death.
<u>Plasmin</u>	<u>Fibrinolysis system</u>	Able to break down fibrin clots, cleave complement protein C3, and activate Factor XII.
<u>Thrombin</u>	<u>Coagulation system</u>	Cleaves the soluble plasma protein <u>fibrinogen</u> to produce insoluble <u>fibrin</u> , which aggregates to form a <u>blood clot</u> . Thrombin can also bind to cells via the <u>PAR1</u> receptor to trigger several other inflammatory responses, such as production of <u>chemokines</u> and <u>nitric oxide</u> .

## Cellular component

The *cellular component* involves leukocytes, which normally reside in blood and must move into the inflamed tissue via *extravasation* to aid in **inflammation**. Some act as phagocytes, ingesting bacteria, viruses, and cellular debris. Others release enzymatic granules which damage pathogenic invaders. Leukocytes also release inflammatory mediators which develop and maintain the inflammatory response. Generally speaking, acute **inflammation** is mediated by granulocytes, while chronic **inflammation** is mediated by mononuclear cells such as monocytes and lymphocytes.

## Leukocyte extravasation



Neutrophils migrate from blood vessels to the inflamed tissue via chemotaxis, where they remove pathogens through phagocytosis and degranulation

Main article: [Leukocyte extravasation](#)

Various leukocytes are critically involved in the initiation and maintenance of **inflammation**.

These cells must be able to get to the site of injury from their usual location in the blood, therefore mechanisms exist to recruit and direct leukocytes to the appropriate place. The process of leukocyte movement from the blood to the tissues through the blood vessels is known as *extravasation*, and can be divided up into a number of broad steps:

1. **Leukocyte localisation and recruitment to the endothelium local to the site of inflammation – involving margination and adhesion to the endothelial cells:** Recruitment of leukocytes is receptor-mediated. The products of **inflammation**, such as histamine, promote the immediate expression of P-selectin on endothelial cell surfaces. This receptor binds weakly to carbohydrate ligands on leukocyte surfaces and causes them to "roll" along the endothelial surface as bonds are made and broken. Cytokines from injured cells induce the expression of E-selectin on endothelial cells, which functions similarly to P-selectin. Cytokines also induce the expression of integrin ligands on endothelial cells, which further slow leukocytes down. These weakly bound leukocytes are free to detach if not activated by chemokines produced in injured tissue. Activation increases the affinity of bound integrin receptors for ligands on the endothelial cell surface, firmly binding the leukocytes to the endothelium.
2. **Migration across the endothelium, known as *transmigration*, via the process of diapedesis:** Chemokine gradients stimulate the adhered leukocytes to move between endothelial cells and pass the basement membrane into the tissues.
3. **Movement of leukocytes within the tissue via chemotaxis:** Leukocytes reaching the tissue interstitium bind to extracellular matrix proteins via expressed integrins and CD44 to prevent their loss from the site. Chemoattractants cause the leukocytes to move along a chemotactic gradient towards the source of **inflammation**.

## Cell derived mediators

\* non-exhaustive list

Name	Type	Source	Description
<u>Lysosome granules</u>	<u>Enzymes</u>	<u>Granulocytes</u>	These cells contain a large variety of enzymes which perform a number of functions. Granules can be classified as either <u>specific</u> or <u>azurophilic</u> depending upon the contents, and are able to break down a number of substances, some of which may be plasma-derived proteins which allow these enzymes to act as inflammatory mediators.
<u>Histamine</u>	<u>Vasoactive amine</u>	Mast cells, basophils, platelets	Stored in preformed granules, histamine is released in response to a number of stimuli. It causes <u>arteriole</u> dilation and increased <u>venous</u> permeability.
<u>IFN-<math>\gamma</math></u>	<u>Cytokine</u>	T-cells, NK cells	Antiviral, immunoregulatory, and anti-tumour properties. This interferon was originally called macrophage-activating factor, and is especially important in the maintenance of chronic <b>inflammation</b> .
<u>IL-8</u>	<u>Chemokine</u>	Primarily macrophages	Activation and chemoattraction of neutrophils, with a weak effect on monocytes and eosinophils.
<u>Leukotriene B4</u>	<u>Eicosanoid</u>	Leukocytes	Able to mediate leukocyte adhesion and activation, allowing them to bind to the endothelium and migrate across it. In neutrophils, it is also a potent chemoattractant, and is able to induce the formation of reactive oxygen species and the release of lysosome enzymes by these cells.
<u>Nitric oxide</u>	<u>Soluble gas</u>	Macrophages, endothelial cells, some neurons	Potent vasodilator, relaxes smooth muscle, reduces platelet aggregation, aids in leukocyte recruitment, direct antimicrobial activity in high concentrations.
<u>Prostaglandins</u>	<u>Eicosanoid</u>	Mast cells	A group of lipids which can cause vasodilation, fever, and pain.
<u>TNF-<math>\alpha</math> and IL-1</u>	<u>Cytokines</u>	Primarily macrophages	Both affect a wide variety of cells to induce many similar inflammatory reactions: fever, production of cytokines, endothelial gene regulation, chemotaxis, leukocyte adherence, activation of <u>fibroblasts</u> . Responsible for the systemic effects of <b>inflammation</b> , such as loss of appetite and increased heart rate.

## Morphologic patterns



A skin ulcer resulting from infection with *Corynebacterium diphtheriae*

Specific patterns of acute and chronic **inflammation** are seen during particular situations that arise in the body, such as when **inflammation** occurs on an epithelial surface, or pyogenic bacteria are involved.

- **Granulomatous inflammation:** characterised by the formation of granulomas, they are the result of a limited but diverse number of diseases, which include among others tuberculosis, leprosy, and syphilis.
- **Fibrinous inflammation:** **Inflammation** resulting in a large increase in vascular permeability allows the blood vessels to pass through fibrin. If an appropriate procoagulative stimulus is present, such as cancer cells<sup>[1]</sup>, a fibrinous exudate is deposited. This is commonly seen in serous cavities, where the conversion of fibrinous exudate into a scar can occur between serous membranes, limiting their function.
- **Purulent inflammation:** **Inflammation** resulting in large amount of pus, which consists of neutrophils, dead cells, and fluid. Infection by pyogenic bacteria such as staphylococci is characteristic of this kind of **inflammation**. Large, localised collections of pus enclosed by surrounding tissues are called abscesses.
- **Serous inflammation:** Characterised by the copious effusion of non-viscous serous fluid, commonly produced by mesothelial cells of serous membranes, but may which also be derived from blood plasma. Skin blisters exemplify this pattern of **inflammation**.
- **Ulcerative inflammation:** **Inflammation** occurring near an epithelium can result in the necrotic loss of tissue from the surface, exposing lower layers. The subsequent excavation in the epithelium is known as an ulcer.

## Inflammatory disorders

Abnormalities associated with **inflammation** comprise a large, unrelated group of disorders which underly a variety of human diseases. The immune system is often involved with inflammatory disorders, demonstrated in both allergic reactions and some myopathies, with many immune system disorders resulting in abnormal **inflammation**. Non-immune diseases with aetiological origins in inflammatory processes are thought to include cancer, atherosclerosis, and ischaemic heart disease.<sup>[1]</sup>

A large variety of proteins are involved in **inflammation**, and any one of them is open to a genetic mutation which impairs or otherwise dysregulates the normal function and expression of that protein.

Examples of disorders associated with **inflammation** include:

- Asthma
- Autoimmune diseases

- Chronic inflammation
- Chronic prostatitis
- Glomerulonephritis
- Hypersensitivities
- Inflammatory bowel diseases
- Pelvic inflammatory disease
- Reperfusion injury
- Rheumatoid arthritis
- Transplant rejection
- Vasculitis

## Allergies

An allergic reaction, formally known as type 1 hypersensitivity, is the result of an inappropriate immune response triggering **inflammation**. A common example is hay fever, which is caused by a hypersensitive response by skin mast cells to allergens. Pre-sensitised mast cells respond by degranulating, releasing vasoactive chemicals such as histamine. These chemicals propagate an excessive inflammatory response characterised by blood vessel dilation, production of pro-inflammatory molecules, cytokine release, and recruitment of leukocytes.<sup>[1]</sup> Severe inflammatory response may mature into a systemic response known as anaphylaxis.

Other hypersensitivity reactions (type 2 and type 3) are mediated by antibody reactions and induce **inflammation** by attracting leukocytes which damage surrounding tissue.<sup>[1]</sup>

## Myopathies

Inflammatory myopathies are caused by the immune system inappropriately attacking components of muscle, leading to signs of muscle **inflammation**. They may occur in conjunction with other immune disorders, such as systemic sclerosis, and include dermatomyositis, polymyositis, and inclusion body myositis.<sup>[1]</sup>

## Leukocyte defects

Due to the central role of leukocytes in the development and propagation of **inflammation**, defects in leukocyte function often result in a decreased capacity for inflammatory defence with subsequent vulnerability to infection<sup>[1]</sup>. Dysfunctional leukocytes may be unable to correctly bind to blood vessels due to surface receptor mutations, digest bacteria (Chediak-Higashi syndrome), or produce microbicides (chronic granulomatous disease). Additionally, diseases affecting the bone marrow may result in abnormal or few leukocytes.

## Pharmacological

Certain drugs or chemical compounds are known to affect **inflammation**. Vitamin A deficiency causes an increase in inflammatory responses<sup>[2]</sup>, and **anti-inflammatory** drugs work specifically by inhibiting normal inflammatory components.

## Termination

The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues.<sup>[1]</sup> Failure to do so results in chronic **inflammation**, cellular destruction, and attempts to heal the inflamed tissue. One intrinsic mechanism employed to terminate **inflammation** is the short half-life of inflammatory mediators *in vivo*. They have a limited time frame to affect their target before breaking down into non-functional components, therefore constant inflammatory stimulation is needed to propagate their effects.

Active mechanisms which serve to terminate **inflammation** include<sup>[1]</sup>:

- **TGF-β** from macrophages
- Anti-inflammatory **lipoxins**
- Inhibition of pro-inflammatory molecules, such as leukotrienes

## Systemic effects

An organism can escape the confines of the immediate tissue via the **circulatory system** or **lymphatic system**, where it may spread to other parts of the body. If an organism is not contained by the actions of acute **inflammation** it may gain access to the lymphatic system via nearby **lymph vessels**. An infection of the lymph vessels is known as **lymphangitis**, and infection of a lymph node is known as **lymphadenitis**. A pathogen can gain access to the bloodstream through lymphatic drainage into the circulatory system.

When **inflammation** overwhelms the host, **systemic inflammatory response syndrome** is diagnosed. When it is due to **infection**, the term **sepsis** is applied, with **bacteremia** being applied specifically for bacterial sepsis and **viremia** specifically to viral sepsis. **Vasodilation** and organ dysfunction are serious problems associated with widespread infection that may lead to **septic shock** and death.

## Acute-phase proteins

**Inflammation** also induces high systemic levels of **acute-phase proteins**. In acute **inflammation**, these proteins prove beneficial, however in chronic **inflammation** they can contribute to **amyloidosis**<sup>[1]</sup>. These proteins include **C-reactive protein**, **serum amyloid A**, **serum amyloid P**, **vasopressin**, and **glucocorticoids**, which cause a range of systemic effects including<sup>[1]</sup>:

- **Fever**
- Increased **blood pressure**
- Decreased **sweating**
- **Malaise**

- **Loss of appetite**
- **Somnolence**

## Leukocyte numbers

**Inflammation** often affects the numbers of leukocytes present in the body:

- **Leukocytosis** is often seen during **inflammation** induced by infection, where it results in a large increase in the amount of leukocytes in the blood, especially immature cells. Leukocyte numbers usually increase to between 15 000 and 20 000 cells per ml, but extreme cases can see it approach 100 000 cells per ml<sup>[1]</sup>. Bacterial infection usually results in an increase of neutrophils, creating **neutrophilia**, whereas diseases such as **asthma**, **hay fever**, and parasite infestation result in an increase in **eosinophils**, creating **eosinophilia**<sup>[1]</sup>.
- **Leukopenia** can be induced by certain infections and diseases, including viral infection, **Rickettsia** infection, some **protozoa**, **tuberculosis**, and some **cancers**<sup>[1]</sup>.

## Systemic inflammation and obesity

With the discovery of **interleukins** (IL), the concept of **systemic inflammation** developed. Although the processes involved are identical to tissue **inflammation**, systemic **inflammation** is not confined to a particular tissue but involves the **endothelium** and other organ systems.

High levels of several **inflammation**-related markers such as **IL-6**, **IL-8**, and **TNF-α** are associated with **obesity**.<sup>[3][4]</sup> During clinical studies, inflammatory-related molecule levels were reduced and increased levels of anti-inflammatory molecules were seen within four weeks after patients began a very low calorie diet.<sup>[5]</sup> The association of systemic **inflammation** with **insulin resistance** and **atherosclerosis** is the subject of intense research.

## Outcomes



Scars present on the skin, evidence of fibrosis and healing of a wound

The outcome in a particular circumstance will be determined by the tissue in which the injury has occurred and the injurious agent that is causing it. There are three possible outcomes to **inflammation**:<sup>[1]</sup>

### 1. Resolution

The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte infiltration cease, and damaged **parenchymal** cells regenerate. In situations where limited or short lived **inflammation** has occurred this is usually the outcome.

### 2. Fibrosis

Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous scarring occurs in these areas of damage, forming a scar composed primarily of collagen. The scar will not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.

### 3. Chronic inflammation

In acute **inflammation**, if the injurious agent persists then **chronic inflammation** will ensue. This process, marked by **inflammation** lasting many days, months or even years, may lead to the formation of a chronic wound. Chronic **inflammation** is characterised by the dominating presence of macrophages in the injured tissue. These cells are powerful defensive agents of the body, but the toxins they release (including reactive oxygen species) are injurious to the organism's own tissues as well as invading agents. Consequently, chronic inflammation is almost always accompanied by tissue destruction.

## Examples

Inflammation is usually indicated by adding the suffix "-itis", as shown below. However, some conditions such as asthma and pneumonia do not follow this convention. More examples are available at list of types of inflammation.



Acute appendicitis

Acute dermatitis

Acute  
infective meningitis



Acute tonsillitis

## Live Blood Under the Microscope

It's true that an individual's life and health energies show in the drops of their blood. Using high powered video microscopes to evaluate the shapes and other properties of individual blood cells can be very revealing. Often things are noticed that are never seen using traditional methods of blood screening. In itself, live blood screening with microscopy is not a diagnostic procedure. However, it can often point you in a direction to take for further diagnostic testing. For our purposes, we simply want to view the "terrain" of the blood to catch a glimpse of the overall "toxic load" and consequent state of health of our client. Of the information that follows in this section, some is found in medical physiology textbooks and is taught in hematology and microbiology classes. Some of the information (particularly that which deals with nutritional aspects of blood morphology) is usually taught to health professionals through continuing education and alternative type programs. As traditional medical and dietetic training is generally inadequate and often based on incorrect assumptions about health, these alternative programs serve as a much needed venue to disseminate this information. It can be controversial. I say controversial because the definitions, findings, causes, and correlations are often the subject of debate. On one hand there is traditional hematology, on the other is standard hematology overlaid on a nutritional framework with different ways of thinking about health and disease. There are varying perspectives of what the observed morphology actually means. Some are correct, some are not. Further complicating matters, many microbiologists seem to work in a vacuum. Three microbiologists may see or have discovered the same thing, but they each call it by a different name. Going further, some biologists have entertained entirely different philosophies. When the serious student of health begins to dig into all aspects of healing, he inevitably unfolds the theories of disease and concepts of microbial pleomorphism as espoused by individuals like Guenther Enderlein. Enderlein was a German microbiologist who did the most extensive and exacting scientific work in this area. I refer to it as the German biological perspective. For purposes of truly understanding blood morphology, this area of study is an absolute necessity. Unfortunately, American hematology and medical students do not get this training. Consequently, the American health system is absolutely ignorant of what is likely the biological reality behind a majority of disease processes. This following material takes you into all of these areas. The intent is to give you a solid foundation in which you can further pursue each area as you desire. The majority of what follows has explanations from standard hematology, expanded views from the medical perspective, and associated thinking and suggested tests that may be run by a traditional medical practitioner (and some tests used by alternative practitioners) if he/she were to have a specific microscopic finding. For the most part, this aspect reflects an allopathic, symptomatic, name the disease mentality which for many cases, is unnecessary for getting a sick patient well. During the workshop, you will have the benefit of instructor clarifications and

expanded insights. Additionally, I've included a brief overview of the "alternative" biological perspective for each microscopic finding. After researching blood morphology for months on end, viewing live blood for untold hours, watching biological relationships unfold, meeting and discussing these issues with other alternative practitioners, it is of my personal opinion that the alternative view is the correct perspective in which to view blood morphology and the biological processes which happen within. Blood references: For the traditional hematological perspective, "Dailey's Notes on Blood", by John F. Dailey; For the alternative biological perspective and insight in the work of Guenther Enderlein, "Blood Examination in Darkfield", by Marie Bleker, "Introduction into Darkfield Diagnostics", by Cornelia Schwedt and Franz Arnoul, and course notes from various workshops. For the more traditional medical view, "The Internist" June 1996, Position Statement of the Council on Diagnosis and Internal Disorders of the American Chiropractic Association.

### **STANDARD HEMATOLOGY - BLOOD BASICS**

Blood is the fluid that circulates through the heart, arteries, capillaries, and veins. It is the chief means of transport within the body. It transports oxygen from the lungs to the tissues, and carbon dioxide from the tissues to the lungs. It transports nutritive substances and metabolites to the tissues and removes waste products to the kidneys and other organs of excretion. It has an essential role in the maintenance of fluid balance. Blood varies in color from an oxygenated bright red in the arteries to a duller red in the veins. The total quantity of blood within an individual depends upon the body weight. A person who weighs 150 lbs. has about 5 quarts of blood in the body. Plasma accounts for about 55 percent of the total volume of the blood. It consists of about 92 percent water, 7 percent proteins, and less than 1 percent inorganic salts, organic substances other than proteins, dissolved gasses, hormones, antibodies, and enzymes. The suspended particles of the blood comprise the other 45 percent of the total volume of blood. They include erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (thrombocytes). Red blood cells originate in the red bone marrow and are stored in the spleen which acts as a reservoir for the blood system. The average red cell has a life of 110 to 120 days. Aged red cells are ingested by macrophages in the spleen and liver. The iron is reclaimed from the dead red cells and then transported by the plasma back to the marrow where it is incorporated into new red cells. The great majority of the cells in the blood are red blood cells. Leukocytes (white blood cells) originate in the bone marrow and lymph tissue. White blood cells are actively engaged in the destruction or neutralization of invading micro-organisms and are then transported to sites of infection and inflammation. For this reason, their life span in the blood is usually very short (a life span of up to 14 days). When infection is present their number are greatly increased and they also become more mobile and move back and forth between the blood, lymph, and tissues. White blood cells come in various shapes and sizes: Granular appearing white cells are known as Neutrophils, which make up about two thirds of all white blood cells; Eosinophils which make up about 2 to 4 percent of the white cell count; and Basophils - which make up less than 0.5 per cent of the white cell count. Non-granular appearing white cells are known as Lymphocytes. These are the natural killer cells and make up about 25-30% of all white blood cells. Two types of lymphocytes T's and B's are involved in immunity. Platelets or thrombocytes are small, clear, disk-shaped bodies about one-third the size of red blood cells or even smaller and play an

important role in blood coagulation and clot formation. One of the most important properties is its self-sealing ability to repair a leak in a blood vessel. The life span of a platelet ranges from eight to ten days.

### **RECORDING LIVE BLOOD - SALIVA pH**

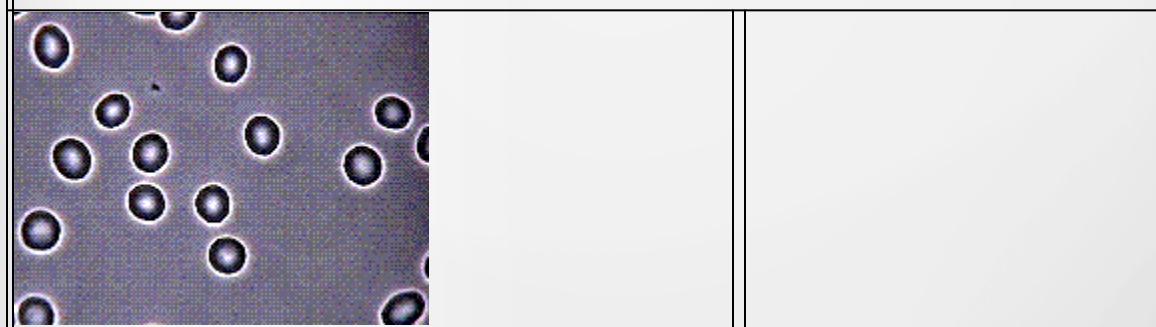
When the blood is brought up on the microscope for study, it is a good time to also take a reading of your clients Saliva pH. You'll remember from the Rot & Rust Workshop (the pre-training session to this course) that pH controls many things in the body. If the pH is off, many bodily processes can also be off. Also, if internal parasite activity (endobiosis) is seen in the blood, it could be that the pH in the blood has been thrown off for some time and it's something you would definitely want to correct. We'll learn more about this when we cover biological terrain. Hours since last meal \_\_\_\_\_ Saliva pH \_\_\_\_\_. In doing this little test, it becomes an appropriate time to introduce simple dietary/pH education. It is also the time to introduce the concepts of "biological terrain" and can set up the patient for more thorough urine/saliva testing. (This assumes you have not already pre-educated your patient and have not yet included the urine/saliva testing as part of your work-up.)

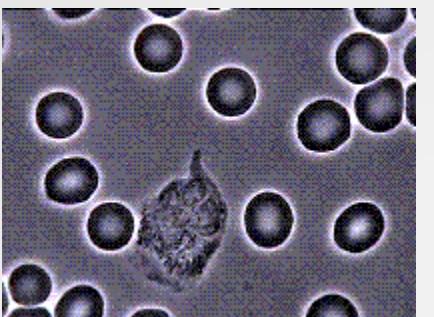
**RED BALL TEST** The red ball test was something given to soldiers during the civil war. If a soldier said he was too sick or weary to fight, he would get his finger pricked with a pin to see if the blood beaded up on the finger or if it was runny with no beading. If it beaded up, the soldier was considered healthy and was given his weapon and sent into battle. If there was no bead, he was sent to the recuperation tents. You can make note of a quick "red ball test" when a drop is taken from the finger. When a drop of blood appears on the finger it should bead up. If the ball is absent it can indicate: -low protein due to: lack of protein in diet, -poor digestion (lack of digestive enzymes), -kidney problems, -anemia (low blood iron.)

### **"READING" LIVE BLOOD**

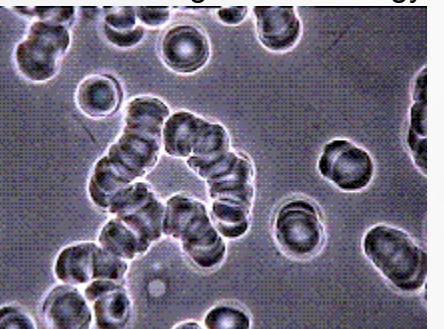
It is absolutely fascinating to watch the play of life at the cellular level. When you see the indicated item or activity listed below, the contributing factors or causes shown are correlated to have been found in most cases. Certainly variations may occur in individual situations. Reading live blood in this fashion can really be considered more of an art than a science. **Remember:** You are not learning a diagnostic procedure for any medical malady. A medical diagnosis *cannot* be made by looking at live blood under a microscope. The real benefit of this procedure is to demonstrate in a very visual way the realities of health to your client which will make a lasting impact and will lock them into understanding and complying with your suggested protocol. That is all.

### **THE PICTURES OF BLOOD**





The red cells are predominately uniform in size and shape and appear as round circles on a gray background. The center of the cells are lightened somewhat and slightly off white in color. They reside freely in their own space, not overlapping or sticking together, but gently bouncing off each other. The white cells (neutrophils) are about as large as two red cells and have a rather grainy appearance with 3 to 4 dark, irregularly shaped lobes inside the cell. Rather than being round, they display many different shapes and are active and moving. In normal blood there are about 700 to 1000 red cells to every white cell. The blood serum surrounding the cells is clear without parasites, bacteria, clots, or other undesired floating masses. Platelets are free floating. **NOTE:** Concerning the names given to the items that follow, the most widely known terms with hematological reference have been listed first. Since we are also studying the pleomorphic reality behind blood elements, the naming convention of Professor Enderlein has also been listed. This will give us more or less a standard which we can use for naming these biological entities. When appropriate an AKA ("also known as") has been added with other biologists terminology. **RED**



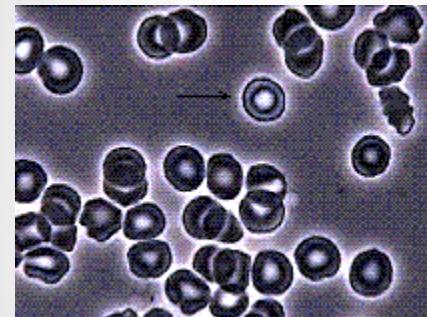
#### BLOOD CELLS - ROULEAU

**ROULEAU** - Stacked RBC's. Worse stage of protein linkage. **CAUSE:** Same as previous page, protein linkage. Often poor protein digestion. The pancreas may be off. Excess dietary protein, poor assimilation. Eating too much animal protein. Blood too toxic (altered blood pH-zeta potential down) from stress, coffee, cigarettes, meat, etc. Dehydration, not drinking enough water (which by the way, is one of the top undiagnosed causes of many ailments). Eating the wrong foods for the blood type, e.g. wheat consumption by type O's, beef consumption by type A's, etc. **SIGNS:** Fatigue, shortness of breath - RBC's cannot carry oxygen; stress on heart. Cold hands/feet - poor circulation. **MED PERSPECTIVE:** Peripheral blood erythrocytes often display the phenomenon of rouleau formation and exhibits a specific role in the pathogenesis of some disease. Plasma fibrinogen and Immunoglobulins are some of the potent rouleau-inducing agents. Some industrial poisons such as benzene, parathion & carbon tetrachloride not only increase this phenomenon but also cause thrombotic and hemorrhagic manifestations as well. Patients suffering from allergies, infections and severe trauma may exhibit rouleau. The presence of massive rouleau can be detrimental to patients suffering from occlusive vascular

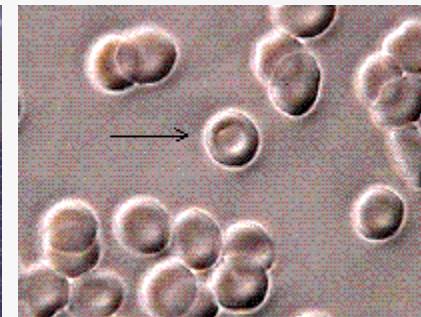
#### RBC

diseases as it causes impairment of blood flow in the small vessels that can compromise the red blood cells ability to exchange carbon dioxide and oxygen gases. This results in localized hypoxia and acidosis as well as generalized fatigue and less than optimum performance. Severe or massive rouleau is not infrequently found in patients with hyperglobulinemia and may be seen in many disease states ranging from arthritis, multiple myeloma, diabetes, myocardial infarction and in patients with increased alcohol intake. The erythrocyte sedimentation rate (ESR) is usually increased because of the increased ratio of mass to surface area resulting in rapid rouleau fallout from the plasma. **ADD'L TESTS:** Cholesterol, Triglycerides, WBC, ESR, SGPT, SGOT, Globulin, A/G Ratio. As rouleau may be caused by acute phase protein elevations in the blood, the possibility of serious disease complications exist when it does not respond to nutritional therapy. If rouleau does not disappear after a maximum of seven days and there is no evident tissue inflammation, tissue damage or tissue necrosis, additional testing can be conducted to rule out arthritis, arteritis disease, choecystitis, cirrhosis, diabetes, endocarditis, rheumatic diseases, rheumatic heart, hepatitis, hyperthyroidism, chronic infection, nephritis, systemic lupus, ulcer, colitis, neoplastic disease. **ALT VIEW:** You will recall that the primary parasitic element of the blood, the endobiont, in its myriad forms, possesses an inherent urge to merge. When red blood cells become infested with the primary parasite, their urge to merge pulls the RBCs together. This accounts for the lemon shapes from the prior page, rouleau formations as shown here, and RBC aggregation as indicated on the next page. **RED**

#### BLOOD CELLS - CODOCYTES (TARGET CELLS)



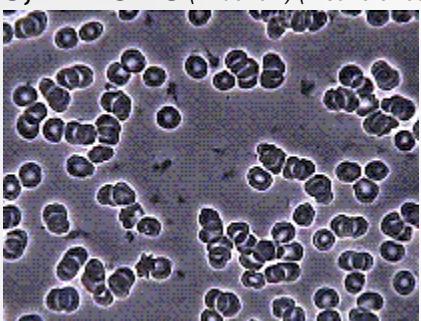
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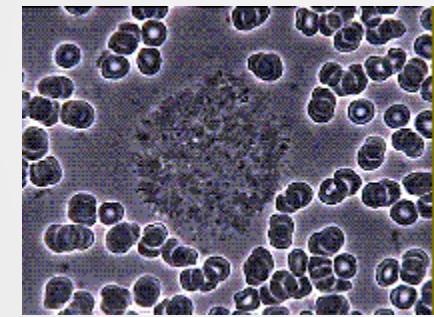
3D Perspective - E.

**APPEARANCE:** These are red blood cells that contain a bright white center encircled by a dark ring that makes it look like a target. The center of the cell does not pulsate or fade in and out, it remains static and bright white. **CAUSE:** May be caused by increased cholesterol and lecithin content, bile insufficiency, liver disease, splenectomy or anemia. The lack of pulsation in the middle of a target cell as opposed to a healthy specimen is due to the fact that the cell membrane has collapsed on itself. This is thought to be due to a lack of iron/hemoglobin. The picture on the right is a more 3 dimensional perspective which better shows the severe concave, donut like nature of a target cell. **SIGNS:** Anemia, tired, low energy. **MED PERSPECTIVE:** Codocytes are erythrocytes that exhibit a dark circular "target" pattern. Marked elevations of target cells is the result of a shift in the exchange equilibrium between the red cells and cholesterol. Conditions that reduce lecithin-cholesterol acetyltransferase production, or interfere with enzyme mechanisms of performance results in elevation of red cell cholesterol and serum phospholipid ratios. Further, the bile salts content ratio in the plasma can affect the exchange between cholesterol and the red cell membrane. Target cells are seen in hypochromic anemia, liver disease and on occasion following splenectomy. Erythrocytes with this configuration are cells lacking iron, therefore any disease process which affects red cell iron absorption may produce target cells. Disruption of hepatic lecithin-cholesterol acetyltransferase production in the alteration of bile acid concentrations due to biliary obstruction can account for increased red cell lipid deposition. The spleen also influences the regulation of erythrocyte lipid content. **ADD'L TESTS:** CBC with differential, serum iron, serum transferrin, serum ferritin, and liver profile (SGPT, GGT, SGOT, LDH, Alkaline phos-phatase). **ALT VIEW:** Target cells have become parasitized by the endobiont.

## PLATELETS; THROMBOCYTES; THECITS (Enderlein) (Also referred to as Colloid



Symplasts when aggregated - Enderlein)



**STANDARD HEMATOLOGY:** Platelets, or thrombocytes, are small, colorless, enucleated bodies. They are produced in the bone marrow by fragmentation of megakaryocytes. Megakaryocytes are large cells found in bone marrow that produce platelets by fragmenting their cytoplasm. Platelets play a vital role in the hemostatic process, which prevents blood loss. When the endothelial lining of a blood vessel is traumatized, platelets are stimulated to go to the site of injury, where they form a plug that helps reduce blood loss. **APPEARANCE:** Platelets are typically very dark to black under phase contrast, are not quite circular, nor square, and range in size from 2-4 microns. **PLATELET EXCESS** - When the platelet count increases the condition is known as thrombocytosis. This may occur in certain disease states such as cancer, chronic infections, and certain blood diseases. It may cause increased blood clot formation. **PLATELET DEFICIT** - When platelet count decreases a condition called thrombocytopenia occurs. This may happen either as a result of decreased platelet production (e.g., bone tumor, chemotherapy) or excessive platelet destruction (e.g., transfusion reaction, immune response). **PLATELET/THROMBOCYTE AGGREGATION.** **CAUSE:** High triglycerides, excessive red meat, stress, caffeine, sodas, chocolate, etc. **SIGNS:** Circulation, capillary blockage, blood clots, heart. **MED PERSPECTIVE:** Severe platelet aggregation can be a potentially serious finding. Platelet aggregation can contribute to cardiovascular disease which is the number one cause of death in the western world. Several organic substances may promote platelet clumping which include collagen, ADP, the catecholamines, certain immune complexes and fatty acids. Cigarette smoking often contributes to "hyperactive" platelet formation. Diabetics and patients with hypercholesterolemia usually demonstrate increased platelet aggregation which can predispose them to clotting disorders which may lead to a vascular thrombus and vessel obstruction. **ADD'L TESTS:** For aggregation rule out high fat diet as cause. If platelet aggregation occurs concurrent with rouleau, acute phase protein elevation caused by inflammation or tissue necrosis or allergy can be suspected. A collagen-damaging disease is possible. If patient does not improve after 30 days of nutritional treatment and dietary management, test and rule out occult disease processes which may cause collagen damage or neoplastic changes. If aggregation exists in absence of rouleau and high fat diet is ruled out, check for excessive stress level producing biochemical imbalance in patient. Other tests -Cholesterol, triglycerides, HDL cholesterol, coagulation time. **ALT VIEW:** Of the concept of fragmenting megakaryocytes producing platelets, it is noted by Enderlein that megakaryocytes have lost their ability of cellular and nucleic division due to massive infestation by the primitive phases of the endobiont.

What mainstream biologists have been viewing as platelets being formed by megakaryocytes through the fragmentation of their cytoplasm, is in fact a process of the endobiotic infestation. For inquisitive biologists, research will show (and has shown) that the ferments from thrombocytes are entirely different from those of human cells, and plant enzymes can be identified on thrombocytes. Platelets are of a pleomorphic nature, and develop as part of the life cycle of the endobiont. They can and do develop beyond the megakaryocyte fragmentation. Only the smaller 2 - 4 micron size are apathogenic. Platelets can grow arm or leg type appendages/filaments, some of which can stretch like a spider web across the viewing field. When platelets begin to grow (which is a function of the terrain) their pathogenicity grows. formed by megakaryocytes through the fragmentation of their cytoplasm, is in fact a process of the endobiotic infestation. For inquisitive biologists, research will show (and has shown) that the ferments from thrombocytes are entirely different from those of human cells, and plant enzymes can be identified on thrombocytes. Platelets are of a pleomorphic nature, and develop as part of the life cycle of the endobiont. They can and do develop beyond the megakaryocyte fragmentation. Only the smaller 2 - 4 micron size are apathogenic. Platelets can grow arm or leg type appendages/filaments, some of which can stretch like a spider web across the viewing field. When platelets begin to grow (which is a function of the terrain) their pathogenicity grows. formed by megakaryocytes through the fragmentation of their cytoplasm, is in fact a process of the endobiotic infestation. For inquisitive biologists, research will show (and has shown) that the ferments from thrombocytes are entirely different from those of human cells, and plant enzymes can be identified on thrombocytes. Platelets are of a pleomorphic nature, and develop as part of the life cycle of the endobiont. They can and do develop beyond the megakaryocyte fragmentation. Only the smaller 2 - 4 micron size are apathogenic. Platelets can grow arm or leg type appendages/filaments, some of which can stretch like a spider web across the viewing field. When platelets begin to grow (which is a function of the terrain) their pathogenicity grows. formed by megakaryocytes through the fragmentation of their cytoplasm, is in fact a process of the endobiotic infestation. For inquisitive biologists, research will show (and has shown) that the ferments from thrombocytes are entirely different from those of human cells, and plant enzymes can be identified on thrombocytes. Platelets are of a pleomorphic nature, and develop as part of the life cycle of the endobiont. They can and do develop beyond the megakaryocyte fragmentation. Only the smaller 2 - 4 micron size are apathogenic. Platelets can grow arm or leg type appendages/filaments, some of which can stretch like a spider web across the viewing field. When platelets begin to grow (which is a function of the terrain) their pathogenicity grows. formed by megakaryocytes through the fragmentation of their cytoplasm, is in fact a process of the endobiotic infestation. For inquisitive biologists, research will show (and has shown) that the ferments from thrombocytes are entirely different from those of human cells, and plant enzymes can be identified on thrombocytes. Platelets are of a pleomorphic nature, and develop as part of the life cycle of the endobiont. They can and do develop beyond the megakaryocyte fragmentation. Only the smaller 2 - 4 micron size are apathogenic. Platelets can grow arm or leg type appendages/filaments, some of which can stretch like a spider web across the viewing field. When platelets begin to grow (which is a function of the terrain) their pathogenicity grows.

# sport

history

pictures on China, AC Milan,  
San Antonio spurs, Dennis Johnson

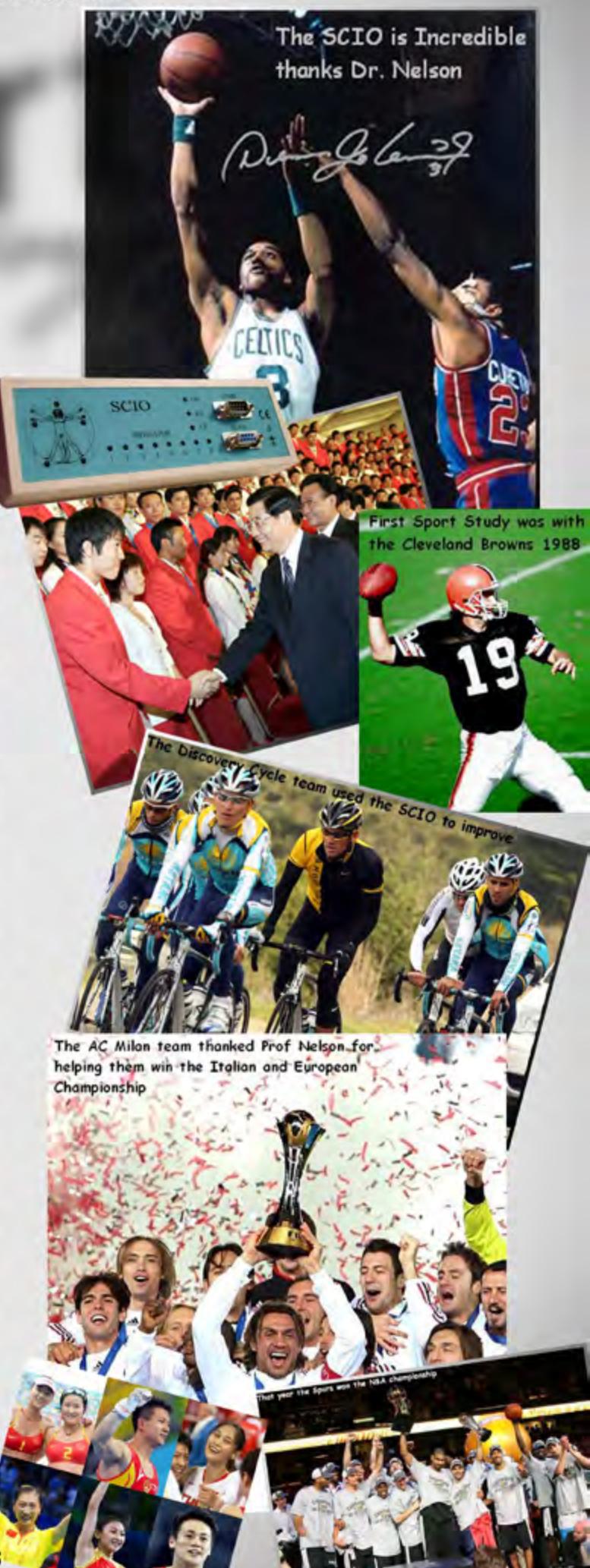
The first sport study with the Quantum Xrroid technology was on members of the Cleveland Browns football team in 1988. The results were amazing and all of the participants went all Pro over the next five years. Having worked with the power lifting team of Hungary in 1991 they went from moderate to gold medal performance.

AC Milan bought some systems and their injury level dropped 91%. This was because the system can stimulate and accelerate healing of injured tissue. They asked for us to develop the device to sharpen the athletic skills of the clients. With this in mind we developed a way to sharpen coordination endurance and strength. AC Milan won the European championship the next two years. We worked with Dennis Johnson ex twice NBA MVP in the San Antonio Spurs system. The results were amazing.

The Chinese Olympic team had us do a study. Out of their 487 athletes in the 2008 Olympic Games, they assigned 150 of the sick, old, weak, and tired to us. The study was to see if we could repair injured tissue and get an athlete back onto the field. The results were astounding. Out of the hundred medals won by the Chinese our 30% of the injured performers won 33 % of the medals. Our athletes were not supposed to win. And because of this 'Desire' was awarded an honorary Gold medal.

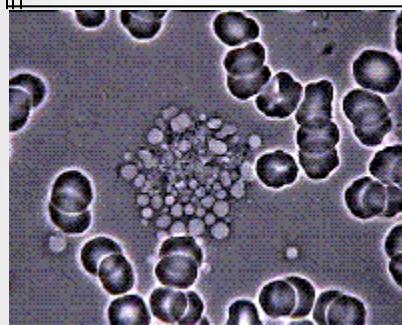
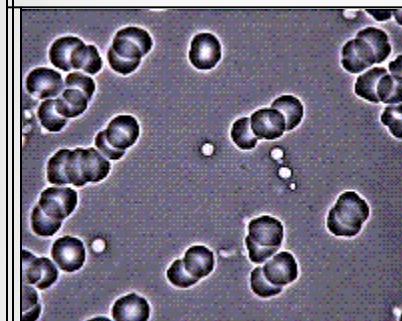
Sports medicine has entered the energetic arena. There are those who want to win and they differ from those who want to conform.

Some of the best cyclists in the world have used the SCIO to win championships



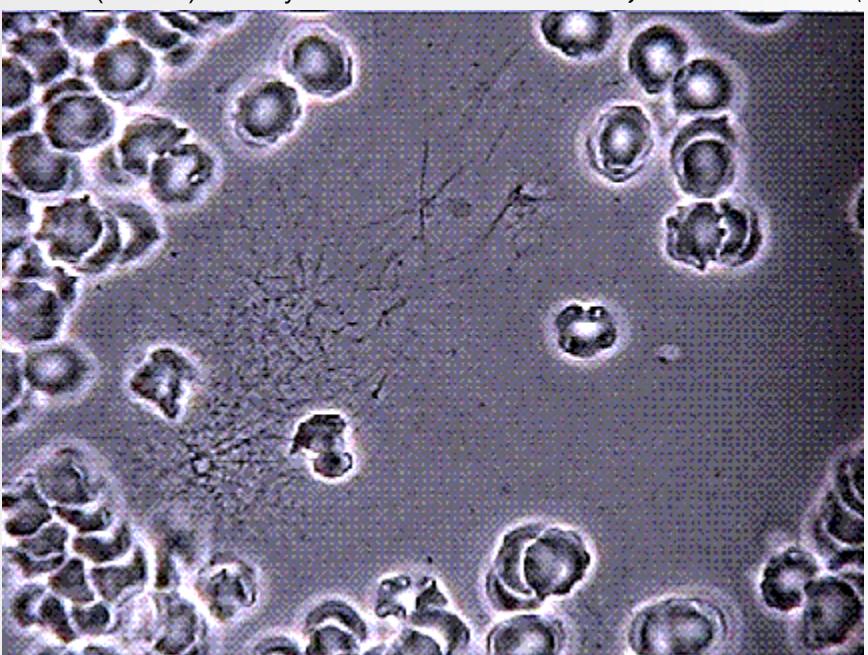
## Live Blood Under the Microscope

### BACTERIAL SPHERES; THECITS (Enderlein)



**BIOLOGY NOTE:** Pleomorphistically considered, all microbes partake in a natural developmental cycle that begins with the PRIMITIVE PHASE (ie. colloid), which is microscopically invisible or visible with difficulty. It proceeds into the BACTERIAL PHASE; and finally will end with a FUNGAL CULMINATION. The fungal culmination can also be replaced by a YEAST CULMINATION. The colloids in your blood will also be heading in a direction. Where they go, how they get there, and the speed with which they arrive, will of course be a function of the terrain which you have provided them through your dietary habits, environmental exposures, thoughts, etc. Many microscopists have called the white round puffy forms as seen in the pictures above YEAST. This drives traditional physicians crazy because they've been taught blood is sterile and yeast cannot be found in the blood. Researchers however have conducted anti-body studies in blood with these forms present and the anti-body tests have definitively read positive for CANDIDA ALBICANS/YEAST (Bradford/Ali, 1994). An alternative view may be held that although anti-bodies may be present, that does not necessarily mean the white forms are specifically yeast. Many contend that the blood is unlikely to hold a conducive pH for yeast growth. However, following the pleomorphic behavior of all bacteria, we know that microbial forms can see a YEAST CULMINATION. If these puffy white microbes were to move out of the blood and take up residence elsewhere in the body, like the interstitium, organs, glands, etc., then indeed they may go in the direction of a yeast culmination - and anti-bodies would certainly be present in the blood as a result. So, if the white forms are not outright yeast, you can consider them as a biological marker for the yeast culmination either happening somewhere in the body currently (more than likely), or the strongest potential for it to happen if the terrain does not change for the better. A parallel situation can be made in regard to elongated gray forms (which will be discussed on the next two pages). Some writers have called them FUNGAL FORMS. But the truth is, if you had fungus in your blood, you'd be dead. However, the potential for FUNGAL

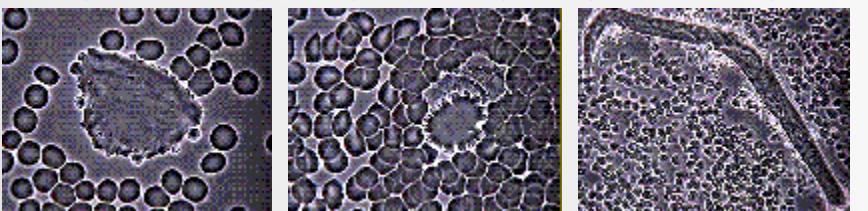
CULMINATION may be very strong, and if the microbe leaves the blood and enters the interstitium, organs, glands, etc. where the pH is different, then indeed that fungal culmination may succeed. Seeing these forms in the blood may be a sign it has already succeeded. The culmination of the fungal form of the endobiont MUCOR RACEMOSUS FRESEN, can easily be obtained through cultivation out of tumor cells. This was accomplished both by Enderlein and Schmitt (Munich) as early as 1903. **SPICULES; FILIT PHASE** (Enderlein)



**SPICULES:**

STANDARD HEMATOLOGY - fibrous (fibrinogen) needles in serum. APPEARANCE: Straight, hair-like formations that look like pick-up sticks in the plasma fluid. CAUSE: Liver stress/toxicity/congestion and associated toxic bowel are suspected when spicules are present. (Spicules could also be a healing indicator if undergoing body cleansing, liver detoxing.) Toxins such as: antibiotics, drugs, alcohol, tobacco, coffee, meat. Plugged/dirty bowel, bowel pH off. Maldigestion and/or bacterial overgrowth can be suspected as cause of bowel toxicity along with old, decaying, impacted fecal matter. SIGNS: Constipation, indigestion, heartburn, bloating, gas, flatulence, fatigue, headaches, backaches. Autoimmune diseases: lupus, MS, MG, Lou Gehrig's. ADD'L TESTS: Evaluate bowel function. Urinary indican test. When alcohol consumption, medication, and bowel toxicity have been ruled out and spicules show no response after nutritionals, liver profile to rule out liver or biliary tract complications. ALT VIEW: Spicules are composed of colloids that have arranged themselves linearly. Their appearance is always due to an excess of colloids in the blood. (Again what are colloids? They are primordial protein substance.) Many spicules (along with RBC lemon shapes, rouleaux and RBC aggregation) is a sign of hyperproteinemia. The thicker their structure, the more densely arranged and complex, the more pathogenicity. As blood sits on the slide and spicules appear with rapidity, the more inflammatory and serious - arthritis, joint problems.

**PROTOPLAST; COLLOID SYMPLAST** (Enderlein) *Spheroplast (denotes protoplast in round formation); Fibrous Thallus (Naessens), Progenitor cryptocides (Livingston-Wheeler).*



**STANDARD**

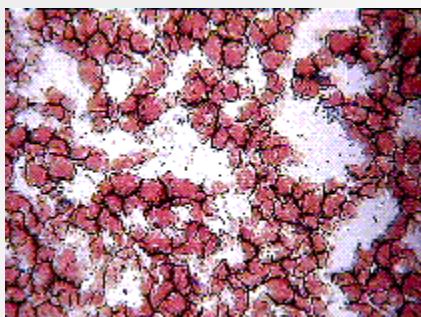
HEMATOLOGY: Cell without a nucleus. Rather large structure in the blood of which much is still not known. Said to be a bacterial parasite which produces toxic by-products (endotoxins);

indicates body is toxic and physically run down; can invade body tissues. APPEARANCE: Looks like a rock in the blood. It can be round, oblong, irregular, or have jagged edges. (The more jagged the edges, the more dangerous the finding.) CAUSE: pH off, low oxygenation, immune system compromised, degenerative disease implications. SIGNS: Fatigue, immune weakness, possible degenerative disease indications. MED PERSPECTIVE: The presence of large numbers of protoplast structures in peripheral blood is an unfavorable sign. Some authors propose they are a collection of progenitor cryptocides (Livingston-Wheeler). Progenitor meaning existing across millenia at the beginning, cryptocides meaning cellular killer. Protoplasts are thought to be related with infectious disease or neoplastic activity and or L-form bacteria. They are thought to be viral in origin. Diseases exhibiting increased numbers of protoplasmic elements are numerous and include neoplastic processes, AIDS, scleroderma and other connective tissue diseases, infectious arthritic conditions and disease processes that impair heart, liver and kidney function. Diabetes has been associated with protoplastemia. ADD'L TESTS: Multi channel 24 blood profile, CBC with differential, thyroid panel, ESR, C-reactive protein, CPK, immunocompetency survey, selected tumor markers, coagulation time. ALT VIEW: Protoplasts are a conglomeration of colloids which develop through the inherent urge to merge which all of the colloids in the blood desire. Given the proper (or more to the point improper) terrain, the colloids will all come together through a dynamic process called symplasm. This is a quantum biological leap where many of the forms instantly combine and become a stable form. AKA: Spheroplast (denotes protoplast in round formation); Fibrous Thallus (Naessens), Progenitor cryptocides (Livingston-Wheeler).

## **Dry Layer Oxidative Stress Test**

Health care practitioners that use a microscope in their practice for patient education have a unique ability to observe the extent of free radical activity taking place in the body. This is through a procedure called the Dry Layer Oxidative Stress Test. It is very simple. A drop of blood from the finger tip is placed on a specimen slide in a series of layers. After the layers dry, they are observed under the microscope. Blood is an interesting indicator of health and where free radicals are concerned, their activity impacts blood morphology. Putting it very simply, when free radicals attack cells, damage is done. The stuff that lies between cells and holds them together is the interstitium, or extra cellular matrix. Through free radical attack, cells get damaged, enzyme activity is altered, and the extra cellular matrix around the cells becomes compromised. Water soluble fragments of this matrix get into the blood stream and then alters the blood clotting cascade. With that done, we find that blood does not coagulate perfectly. This is one mechanism for altering a "normal" blood pattern. Reading the dry layers of blood is like reading an ink blot. It can be very revealing as to the overall state of one's health. Blood from a healthy person will be uniform in coagulation, and tightly connected. From an individual with health problems and excess free radical activity, the dry layer blood profile will be disconnected, showing puddles of white (known as polymerized protein puddles). The more ill the patient with free radical/oxidative stress, the more disconnected is the dried layer of blood.

## MEDICINE FOR THE NEXT MILLENNIUM



The image on

the left is a dried layer of blood of a healthy individual. Notice how it is inter-connected with black connecting lines. The black interconnecting lines is a fibrin network. This is fibrinogen, one of the protein constituents of the blood. The red in-between the black lines are the red blood cells. The image to the right is of an individual who has cancer. Notice how the blood fails to coagulate completely and has many white areas. These are the polymerized protein puddles and they reflect oxidative stress. They represent the degradation of the body's extra cellular matrix from free radical activity. Since free radical activity has been implicated in nearly all disease processes, this test can be used as a quick reference to gauge the severity and extent of one's health problems. Researchers have discovered certain biochemical pathways which create the free radical pathologies and leave their tell tale signs in the dry layer footprint of blood. Depending upon the nature of the degenerative disease, various patterns in the blood will unfold based upon the modifying substances inherent within that particular disease process. It is in this way that the dry layer oxidative stress test not only reveals the presence of free radical activity, but the nature of the disease which has resulted from that activity. The most powerful aspect of this particular tool for any doctor is to assess whether the patient is really getting better, or whether their symptoms are just getting pushed around. When a patient is truly getting better, the doctor knows definitively through this microscopic examination. In the case of the cancer profile above, as the patient reverses their disease process, the white puddles will begin to fill back in with red blood cells. Subsequent tests will illustrate this event happening. If the patient is getting worse, the pattern will continue to degenerate. There are many things you can learn from these tests. Just like reading live blood, reading dry layers can be considered an art. There is much more research, peer review and corroborated studies that need to be done in this area. During this part of the course we will be using the "Oxidative Stress Test (OST)" scorecard. Under most of the indications, questions or causes are listed that can be pursued with the patient. These are listed to help point you in the right direction for a future diagnosis, or corroborate an existing diagnosis. As we study this technique, we will go over the score card, blood gathering technique, special microscope set-up, and the color blood prints. We will begin with an oral discussion of the theory of the test and will review the front page of the scorecard. We will then continue with the detail of the test as reviewed in the workbook. The blood slide preparation and microscope procedure will be given as hands-on learning in class.

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### MEDICINE FOR THE NEXT MILLENNIUM

AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
2. Changes Inside of RBC	Target Cells C1	Low O2, B12, folic Acid, anemia, insufficient bile, obstructive jaundice Low iron or reduced hemoglobin synthesis, heavy menstruation, ulcers hypothyroidism, spleen dysfunction Dysbiosis, pale skin, lethargy, long airplane travel less than 72 hours, thalassemia, nagging fatigue	Veg. Enzymes, iron, folic acid B6, 12, green foods, liver glandular, HCL taurine, N-Acetyl cysteine, Black, strapmolasses, wheat germ, Kelp, black radish, Pancreatin, choline, Inosito Muchokehl w/ Alkala Sanuvis CBC
	Inclusions in RBC (Parasitized) C2	Stressful lifestyle, appear 18-24 months before clinical symptoms, yeast infections, terrain imbalance, pH of saliva acidic dysbiosis, acute and chronic disease skin fungal issues	Stress Management Flora inoculation, 714-X, QXCI Pantothenic acid, propilis B6, Spleen glandular, Vit. A, B6, Mucokehl & Alkala, pH blood 7.35
	RBC appear rough & thorny (Echinocytes) C3	Increasing dysbiosis, liver spleen issues, impaired O2 delivery	Free radical scavengers, selenium, Raw spleen Liver concentrates, B Complex, PABA, enzymes, Vit. C pH buffered, Vit. E Mucokehl & Alkala
3. RBC Formations	Rouleau D1	Hyperviscosity of blood, dysbiosis hyperproteinemia, intestinal stress multiple myeloma, congestion, mental and physical stress, low O2 poor digestion, in asymmetric protein molecules, more serious if mixed with fibrin, mineral deficiencies geopathic, chemical, radiation, stress poor circulation, cold hands and feet	Proper nutrition, flora, pH, Stress i due to Dysbiosis use Mucokehl Latensin, Utilin, Pefrakehl, Sanuvis, HCL niacin, Enzymes, cayenne Tract minerals, B3, pancreatin Drainage of liver, lymph, kidney, Leaky Gut Protocol, calcium lactate pancreas, Tahebo tea, lemon Water, Ozone, DNA Repatterning
	Aggregation D2	Saturated fat ingestion, Inhibits O2 & CO2 transfer pH and electrolyte and trace minerals and enzyme imbalance, poor excretion ELF/EMF exposure, heavy metals intake of toxic foods, liver issues, long term stress, extreme heat stress, shortness of breath, joint pain, blood pH alkaline Toxic foods, at risk of CVA	Backing soda baths, pertin fermented foods, spiruline, B3, B6, Cayenne EFA, raw foods, HCL & pancreatin Vit. E, Cell food, Celtic Salts Enzymes, Potassium citrate, QXCI flax oil, QXCI, niacin, DNA Repat. Trace minerals, ozone, chelation, Licorice root, organic foods Alkala, & Sanuvis & Nigersan Mucokehl & HCL in IV form
4. White Blood Cells	Too few E1	Inadequate immune response, radiation, chemotherapy, free radicals	CBC, Ozone, Blood transfusions, IV Therapies
	Too many E1	Infection, digestive issues, look for kloekothecits, allergies, Hodgkin's Leukemia	CBC, Vit C IV, HCL, pH Sanum
	Viability below 75% E2	Bacterial, fungal, viral infections, Chronic fatigue, smoking, hypoxia, Low HCL, B12, C and zinc, increase sugar intake, candida, fungus, digestive insufficiency Sugar intake	Raw thymus, grapeseed, Vit. C Ozone therapy & peroxide baths, HCL & pepsin with meals Sanum Candida protocol Super oxide dismutase SOD trace minerals, enzymes
	Parasitized WBCs (Enderlein) (Eosinophils) E3	Non seroidal drugs, hypoxia of bowel silver fillings, dysbiosis, leaky gut, leukemia, parasite infection, impaired cellular defense, Hodgkin's more than 1-3% means allergies dark circles under eyes, white spots on finger nails, eczema, fluid retention	Rebas, Latensin, recarcin, Omege testing, for foods, parasites, BTA, Spenglersan test for candida, Vit. A, C B6, Zinc
	Hypersegmented WBC E4	HCL, B12, folic acid, poor immunity, chemotherapy, chronic deg. Diseases, Malabsorption, glossitis, magenta red tongue, depression, menopausal issues, at risk of heart attack	SOD, mineral analysis for Zinc Copper manganese, Green Leafy veg. Legumes spinach, B12, HCL
	Lysing WBC E5	Immune compromise, cortisone use Lymphatic issue, geopathic stress B12, Folic acid imbalance dental foci, copper pipes, heavy metals assimilation and digestion issues	Enzymes, pH balance see viability above Omege re heavy metals Spanglersan

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AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
5. Fibrin	Thick Spider web formation Or bouquets F1-F4	Dysbiosis, liver kidney stress, Cancer, heart disease, bowel toxicity Oxidative damage in blood, fatigue Arthritis, joint & rheumatic issues connective tissues issues, brain fog, stress to mesenchyme, malabsorption congestion, in O2, flatulence, hypertensive drugs, antibiotics use heart bloating, antihistamine use, headaches, Tylenol use, degenerative & Chronic diseases Lupus, MS, MG, ALS (tuberculosis disorders), alcohol, virus	pH balance, homeopathic drainage, bowel cleanse, EFA, BTA, Spenglersan, Drink water 8 glasses, HCL, vigorous exercise/walks, enzymes, Potassium Citrate Trace minerals, Vit. Bs Mucokel, Nigersan, & Atox Alkala, Sanuvis, Kambucha tea green foods, Bifidus etc. juice fast, licorice, Salmor oil
6. Platelets	Platelets not visible with NaCl	2ndary defense readiness impaired Aggregation G1-G3	Balance pH, BTA Enzyme, digestive support CBC & HDI balance pH, ozone, GIA, DHA Triglycerides, stress, cold hands, feet O2, inc. chylous material Upward mobility of Mucor (congestor) Diabetes, viral infections including Epstein Barr, Herpes, Hep.C, Angina Niacin & magnesium deficiencies Low consumption of fruits & veggies At risk of CVA, and clots, liver stress Poor circulation, high blood pressure Atherosclerosis, degeneration of arterial wall, dec. energy, pain in claves When walking, progressive cancer Current EDTA chelation, ozone, H202
7. Pleomorphic changes	Somatids/Protits Too few H1	RBC membrane too thick, does not Allow somatids/Protits to emerge Too alkaline blood pH, defense weak	Regulate pH, mineral salts, Viatmins hormones, enzymes, metals Mucokel & Nigresan
	Too Many = Protit Veil H1	Acid pH in tissue & alkaline in Blood During isopathic therapy Abundance of protons	Blood pH=7.35 for sperm formation Alkala & Sanuvis regulate pH before starting isopathic or other remedies detox kidney of heavy metals
	Too Many Chylomicrons	Highest 2-6 hrs. after fatty meal Digestive organ issues High blood pressure, poor fat digestioon Pancreatic insufficiency, obesity Leaky gut, high blood fats, Or liver issues	Fasting blood raw food, liver & spleen concentrate, Vit B & folic acid, Vit. C, lipotropics, homeopathic drainage bowel detox, enzymes, saturated fats lecithin EFA
	Macrosympotits (embryonic Bacteria) H2	Acid pH in tissue & alkaline in Blood Immune dysfunction, use of antibiotics Fermentation digestive process Anaerobic condition, NSAIDS cold hands, feet, poor circulation depression, Myalgias, abdominal pain, cognitive & memory deficits, Leaky gut, inflammatory bowel, enterocolitis, Crohn's, Ankylosing Spondylitis, acne, eczema, psoriasis, cystic fibrosis, celiac disease, food * chemical sensitivities, antibiotic use dental foci = Strp Inf. Environmental illness, flora unbalanced higher Endobiosis,	Alkala & Sanuvis regulate pH Ozone Therapies, detox liver Address digestive issues QXCI for food sensitivities intestinal flora DNA Reptattering Notakehl to unlock All B Vits., retinal, ascorbate, tocopherol, zinc, selenium, molybdenum, manganese, EFA, magnesium, glutamine, Glutathione, flavanoids, fiber Spenglersan Mucokel * Nigersan or Sankombi
	Pteroharpen (dy protein) H7	Excessive undigested protein in blood related to heart disease, recurrence of disease, asthma arthritis	Enzymes, dietary changes, Nigersan balance pH, raw & green food replace animal protein, Citrokehl Spenglersan, pancreatin, HCL
	Yeast Like Forms Naessens CWD (Cell Wall Deficient) H3	Related to acute & chronic infections can be induced by ultra violet light & penicillin, If pH more and more acidic will develop further resistant to antibiotics & germicides anaerobic terrain, ingest amino acids	Bio-oxidative therapies, Intestinal flora milieu therapies, propolis Vit. BC, A, B5, 6, & D, Thymus glandular, Zinc, Garlic, Colloidal silver Homeopathic drainage Bowel cleans, olive leaf extract

AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
		Leaky gut syndrome, compromised Intestinal flora, antibiotic therapies Feed on toxins, undigested nucleic acids And lipids, chemicals, high blood sugar Colds, earaches, boils	Mucokel & Alkala 714 - X, zinc absorption issues, Echinacea
	Colloid (transparent balloons) no Nuclei inside, when have 4-7 mychits Act as Thrombocytes, & Dioekothecits (2nd defense) H4	Regulator of immune response To make spermits, colloids and Macrosympotits	pH of blood has to be 7.35 QXCI
	Thecits with 1-3 or more than 7 Nuclei (Mucor bacteria) called an Ascus (Naessens) is a Thecit with more Than 9 nuclei H5	Mirrors candida Fermentation process, Leaky Gut Foci in mouth, chronic disease Cancer, clogged lymph	714-X Candida: Colloidal Silver intestinal flora, Utilin, notakehl, w/ Alkala, Ozone, Albicansan, Fortakehl, Denta foci Pefrakehl, Spenglersan, pH balance
	Bacterial Rods (higher the Development the more the pathology) H6	Virus is a species specific chondrit Tumors. Dental foci, if in Abdomen can Become Peritonitis, if in the stomach can Become appendicitis, myeloma & Diabetes, muddled thinking	Mucokel, Alkala, pH balance Oxygen therapies, Zinc, Intestinal flora, Spenglersan, Propolis, thymus, Vit. A, C
	Ascits & Synascits (from Mychits) May look like flimmering in RBC When slide crushed ascits will emerge if present. H6	Not seen in healthy blood Even days later, precancerous Oral pathology, silver, root canals Bridges, crowns, caps, Alzheimer's, Parkinson's, MS	Needs spermits to copulate with mucus Mucokel, pH balancing Enzymes Remove dental foci Spenglersan
8. Crystals	Hinder circulation to brain & heart Includes heavy metal toxins, White & White-Yellow	Kidney stress, liver stress Sclerotic chunks, inadequate lipase Metabolism, undigested protein Inflammatory process, capable of Pleomorphic development, resistant to Competitors in environment	Homeopathic drainage, Raw & green food, trace minerals Hydrate body flush the cells Raw liver & spleen concentrate Raw animal & veg. Fats, Vit. Bs, C Folic acid, fiber blend
	Yellow-Red	Tuberculosis	Enzyme therapies Utilin = drainage Drain/detox kidney Utilin upper body focus Notakehl & Nigersan = lower body Spenglersan Liver drainage + Latensin & Taraxicum & Chelidonium Ozone Therapy
	Trapezoid, broken glass	Poor digestion of fats, or chelation	Nigersan Fiber & raw & green foods Colonics, flora replacement digestive enzymes
	Steel-Blue with small red rim	Tuberculosis	
	Brown or Brown-Yellow	Upper Abdomen, liver, gall bladder	
	Yellow-Blue -Green	Urogenital issues, pre-noplastic stage Tylenol	
	Blue reflection, Cornflower Blue	Metabolic Disturbance and/or Aspergillus, Thyroid, pesticides	



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## SUMMARY OF SANUM THERAPY IN 4 STEPS According to Dr. Konrad Werthmann

### MILIEU

(Terrain)

ALKALA pH  
SANUVIS for toxins of mucor  
CITROKEHL for toxins of aspergillus

### INFAMMATION

NOTAKEHL for staph/strep  
FORTAKEHL for gastritis, chlamydia  
QUENTAKEHL for detox virus  
ALBICANSAN for candida  
PEFRAKEHL for inf. in offices  
EXMYKEHL for candida, pancreas

### BASICS

MUCOKEHL mucor  
NIGERSAN aspergillus  
SANKOMBI children & elderly  
MUCEDOKEHL limbic, microcirculation  
RUBERKEHL URT & LRT

### IMMUNOBIOLOGICAL REMEDIES

RECARCIN for joints, spondylitis  
LEPTUCIN for artery wall elasticity  
LATENSIN for depression glands  
ARTHROKEHLAN A degenerative  
ARTHROKEHLAN U head throat inf.  
SANUKEHLS for specific microorganisms  
UTILIN allergy colitis  
UTILIN S Inherited TB

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9. Symplasts, Protoplasts	Colloid J1	Degenerative diseases, toxemia Excess Colloids, nutritional reserves, Toxins, dysregulated Endobiont The harder the symplast the more	Alkala, Sanuvis, Citrokehl, Mucokelhi Nigerian
	Thrombocyte & Leukocytes Eltorous Thallos (Nascentes) J2	Pathogenic, High blood alkalinity From Fibrin, retics, excess ammonia Growth hormone - chronic diseases Radiation, chemotherapy	Dissolve w/ Mucokelhi & Nigerian &/or Sankombi pH balance, ozone, 714-X, Blue Lite
	Protoplasts (grey-white outline) With red crystals J3	Bacterial & fungal cell with plasma Membranes, immune competence, tooth, Dysregulated terrain, urogenital, colds Extreme bowel toxicity, strep. Mutans Degenerative condition Fatigue, liver & kidney dysfunction, Breeding ground for bacterial infection	Vit. B5, 6, A, D, & C Thymus, adrenal & spleen Glandular Zinc, Intestinal flora, Echinacea Pancreatin colostrum, Spenglerian Maculkehl, Alkala, Nigerian
10. Sylogeny	K 1	Unification of protein colloids of the Endobiont & different developmental stages, to attain a stable form, of multiple species. Terrain anaerobic, fermentation	Balance pH, Nigerian, Ozone

### RECOMMENDATIONS:

Health Trend: ILL HEALTH      HOMEOSTASIS      HEALTH  
10 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 10

EVALUATION: 0-20min. Negative  Positive  Blood Degradation Negative  Positive   
Potential Disease Factors:  
Mucor Racemosus      Aspergillus      Leaky gut      Candida/Fungus      Toxins      Teeth  
Recommended Action:  
Mucokelhi & Atox      Nigersan & Atox      Sankombi      Sanuvis      Citrokehl      Utilin'S\*      Fortakehl  
Alkala      Streptococcus      Staphylococcus      Rebas      Latensin      Recarcin      Albicansan      Pefrakehl      Notakehl      714-X  
Secondary Defence System: Strong  Weak  Absent   
Next Appointment: 3 months  6 months  12 months  After Treatment Started

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	Yeast like Forms Nisseria CWD (Cell Wall Deficient) H3	Related to acute & chronic infections can be induced by ultra violet light & penicillin, if pH more and more acidic will develop further resistant to antibiotics & germicides, anaerobic terrain, ingest amino acids Leaky gut syndrome, compromised Intestinal flora, antibiotic therapies Feed on toxins, undigested nucleic acids And lipids, chemicals, high blood sugar Chol, carboes, boils	Bio-oxidative therapies, Intestinal flora milieus therapies, propolis Vit. BC, A, B5, 6, & D, Thymus glandular, Zinc, Garlic, Colloidal silver Homeopathic drainage, Bowel cleanse, olive leaf extract Mucokel & Alkals 714-X, zinc absorption issues, Echinacea Blue Lite
	Colloid (transparent balloons) no Nuclei inside, when have 4-7 mychits Act as Thrombocytes, & Diseokothrocyts (2 <sup>nd</sup> defense) H4	Regulator of immune response To make spermatozoids, colloids and Macrozymoprotids	pH of blood has to be 7.35 Alkals, Sanguis Chirokels
	Thects with 1-3 or more than 7 Nuclei (Mucor bacteria) called an Ascos (Nisseria) is a Thect with more Than 9 nuclei H5	Mucors Candida Fermentation process, Leaky Gut Poli in mouth, chronic disease Cancer, clogged lymph	714-X, Blue Lite Candida protocol, Colloidal Silver intestinal flora, Utilin, Notakel, w/ Alkals, Ozone, Allicinasan, Fortakel, Dental foci, Peleakel, Spenglerian, pH balance
	Bacterial Rods (higher the Development the more the pathology) H6	Virus is a species specific eboodit Tumors, Dental foci, if in Abdomen can Become Peritonitis, if in the stomach can Become appendicitis, myeloma & Diabetes, muddled thinking	Mucokel, Alkals, pH balance Oxygen therapies, Zinc, Intestinal flora, Spongiansan, Propolis, thymus, Vit. A, C
	Ptersharpens H7	Too much undigested animal protein in the blood, higher endobiosis	Decrease animal protein consumption 714-X, Blue Lite, Sanguis Therapies
	Acids & Synapses (from Mychits) May look like shimmering in RBC When slide crushed acids will emerge if present. H8	Not seen in healthy blood Even days later, precancerous Oral pathology, silver, mol canals Bridges, crowns, caps. Alzheimer's, Parkinson's, MS	Needs spermatozoids to copulate with nuclei Mucokel, pH balancing Enzymes, 714-X, Blue Lite Remove dental foci, w/ sanguis Spenglerian
8. Crystals	Hinder circulation to brain & heart Includes heavy metal toxins, White & White-Yellow 11	Kidney stress, liver stress Sclerotic chunks, inadequate lipase Metabolism, undigested protein Inflammatory process, capable of Pleomorphic development, resistant to Competitors in environment Terrain issues clusters=virus	Homopathic drainage, Raw & green food, trace minerals Hydrate body flush the cells Raw liver & spleen concentrate Raw animal & veg. Fats, Vit. B6, C, Polio acid, fiber blend Sanguis, Chirokels, Mucokel, Nigerson, Sankombl
	Yellow-Red 12	Tuberculosis	Enzyme therapies
	Trapezoid, broken glass 13	Poor digestion of fats, or chelation	Utilin - drainage Oxidized detox kidney
	Steel-Blue with small red rim 14	Tuberculosis	Utilin upper body focus
	Brown or Brown-Yellow 15	Upper Abdomen, liver, gall bladder	Notakel & Nigerson - lower body
	Yellow-Blue-Green 16	Lingering issues, pre-neoplastic stage Tylenol	Spenglerian Liver drainage + Latensin & Taraxicum & Chelidonium Ozone Therapy
	Blue reflection, Cornflower Blue 17	Metabolic Disturbance and/or Aspergillus, Thyroid, pesticides	Nigerson Fiber & raw & green foods Coliotics, flora replacement digestive enzymes
	Red-Yellow 18	Bowel/liver toxicity, constipation, infection, elevated BP, Plaque, pancreas Clogged arteries, uric acid, A1S, MS Connective Tissue Disorders TT Prescription drugs, require change in glasses, skin eruptions, toxic foods Putrefaction in bowels, leaky gut Chronic Fatigue, Epstein Barr, Herpes Drug users, cancer, junk food, candida	
	Square crystals 19	Neurological problems	MKOVACS revised 2008

AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
5. Fibre	Thick Spider web formation Or bouquets H1-H4	Dysbiotic, liver kidney stress, ↓ sleep Cancer, heart disease, bowel toxicity Oxidative damage in blood, fatigue Arthritis, joint & rheumatic issues connective tissue issues, brain fog, stress to mesenchyme, malabsorption congestion, ↓ in O2, fluctuation, hypertensive drugs, antibiotics use heart blocking, antihistamine use, headaches, Tylenol use, degenerative & Chronic diseases Lupus, MS, MG, FM, CF, AFS (tuberculosis disorders), alcohol, virus, Kidney excretion issues	pH balance, homeopathic, drainage, bowel cleanse, EPA, Spenglerian, Glutathione, Bio-Lac Drink water & glasses, HC1+, vigorous exercise/walks, enzymes, Potassium Citrate Trace minerals, Vit. B Mucokel, Nigerson, & Ater Alkals, Sanguis, Kanobucha tea green foods, Bifidus etc. juice fast, licorice, Salmon oil Rub Mucokel into painful Joints, Inject Mucokel along spine, Use Mucokel for Bouquets
6. Platelets	Platelets not visible with NaCl	2ndary defence readiness impaired	Balance pH.
	Aggregation G1-G3	pH imbalance, excess protein, toxic foods, Triglycerides, stress, cold hands, feet, ↓ O2, inc. chylous material Upward mobility of Mucor (congestive), Diabetes, viral infections including, Epstein Barr, Herpes, Hep C, Angina, Nicotin & magnesium deficiencies, Low consumption of fruits & veggies, At risk of CVA, and clots, liver stress, Poor circulation, high blood pressure, Atherosclerosis, degeneration of arterial wall, dec. energy, pain in calves, When walking, progressive cancer, Current EDTA chelation, ozone, H202	Enzyme, digestive support CBC, balance pH, ozone, DHA, + stress SCIO, lecithin, omega 3, greens, Vit B & C, raw fresh fats, L-Carnitine, Fish, EPA chelation, N- Acetyl cysteine potassium Magnesium Aspartate, B6, 12 Cayenne, homeopathic drainage, colon cleanse, Doppler, IV of HCl & Mucokel, chelation Alkals, Mucokel if B12 high, Sanguis, Mucokel millet therapy, Enzymes, Milk thistle diet GLA, Lipotropics, Vit. B6, E, Chromium, Echocardiogram * Exercise, Glutathione, Bio-Lac
7. Pleomorphic changes	Somatids/Protids Too few H1 Too Many - Frost Vell	RBC membrane too thick, does not Allow Somatids/Protids to emerge Too alkaline blood pH, defence weak	Regulate pH, mineral salts, Vitamins hormones, enzymes, metals, Bio-Lac Mucokel & Nigerson
	H1	Acid pH in tissue & alkaline in Blood During isopathic therapy Abundance of proteins	Blood pH 7.35 for spermatozoid formation Alkals & Sanguis regulate pH before starting isopathic or other remedies detox kidney of heavy metals
	Too Many Chylomicrons	Highest 2-6 hrs. after fatty meal Digestive organ issues High blood pressure, poor fat digestion Pancreatic insufficiency, obesity Leaky gut, high blood fats, Or liver issues	Fasting blood raw food, liver & spleen concentrate, Vit B & folic acid, Vit. C, Lipotropics, homopathic drainage bowel detox, enzymes, ↓ saturated fats, lecithin EPA ↑ fibre
	Macrosymptids (embryonic Bacteria) H2	Acid pH in tissue & alkaline in Blood Immune dysfunction, use of antibiotics Fermentation digestive process Anaerobic condition, NSAIDS cold hands, feet, poor circulation depression, Myalgia, abdominal pain, cognitive & memory deficits, Leaky gut, inflammatory bowel, enterocolitis, Crohn's, Ankylosing Spondylitis, acne, eczema, psoriasis cystic fibrosis, celiac disease, food * chemical sensitivities, antibiotic use dental foci = Strep Inf. Environmental illness, flora unbalanced higher Endobiosis.	Alkals & Sanguis regulate pH, BIO-lac Ozone Therapies, detox liver Address digestive issues, Bio-Lac SCIO for food sensitivities, intestinal flora DNA Repatterning Notakel to unlock All B Vitas, retinol, ascorbate, tocopherol, zinc, selenium, molybdenum, manganese, EPA magnesium, glutamine, Glutathione, flavonoids Spenglerian Mucokel * Nigerson or Sanguis
			MKOVACS revised 2008

AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
2. Changes inside of RBC			
	Target Cells C1	Low O2, B12, folic Acid, anemia, insufficient bile, obstructive jaundice Low iron or reduced haemoglobin synthesis, heavy menstruation, ulcers, haemorrhoids hypothyroidism, spleen dysfunction Dysthrosis, pale skin, lethargy, long airplane travel less than 72 hours. Thalassemia, nagging fatigue. Colon CA, Duodenal ulcers	Veg. Enzymes, Bio-Lac, iron, folic acid B6, 12, green foods, liver glandular, HCl, taurine, N-Acetyl cysteine, Glutathione, Blackstrap molasses, wheat germ, Kelp, black radish, Pancreatin, choline, Inositol, Mucolohil w/ Alkalai, Sanavis, Bio-Lac CBC, Yoga nostril Breathing
	Inclusions in RBC (Parasitized) C2	Stressful lifestyle, appear 18-24 months before clinical symptoms, yeast infections, terrain imbalance, pH of saliva acidic dysbiosis, acute and chronic disease skin fungal issues, nagging fatigue	SCIO for Stress Management Flora inoculation, Bio-Lac, 714-X, Blue Lite Pantothenic acid, propolis B6, Spleen glandular, Vit. A, B6, Mucolohil & Alkalai, pH blood 7.35
	RBC appear rough & thorny (Echinocytes) C3	Increasing dysbiosis, liver spleen issues, impaired O2 delivery	Glutathione, selenium, Raw spleen Liver concentrates, Vit. E, Blue Lite B Complex, PABA, enzymes, Vit. C pH buffered, Methionine, N-Acetyl Cysteine, Mucolohil & Alkalai
3. RBC Formations	Redness D1, D6	Hyperviscosity of blood, dysbiosis hyperproteinemia, intestinal stress multiple myeloma, congestion, mental and physical stress, low O2 poor digestion, ↑ in asymmetric protein molecules, more serious if mixed with fibrin, mineral deficiencies. Geopathic, chemical & radiation stress, poor circulation, cold hands and feet, dehydrated	Proper nutrition, flora, pH, ↓ Stress if due to Dysbiosis use Mucolohil Latendin, Utilin, Peptakehl, Sanavis, HCl niacin, Enzymes, cayenne Trace minerals, B3, pancreatin Drainage of liver, lymph, kidney, Leaky Gut Protocol, calcium lactate pancreas, Tahebo tea, Lemon Water, Ozone, DNA Repairing, H2O2 baths ↑ Water, RTRE
	Aggregation D2	Saturated fat ingestion, inhibits O2 & CO2 transfer pH and electrolyte and trace minerals and enzyme imbalance, poor excretion ELF/EMF exposure, heavy metals intake of toxic foods, liver issues, long term stress, extreme heart stress, shortness of breath, joint pain, blood pH alkaline Toxic foods, at risk of CVA & blood clots, ingestion of nightshades especially GMO potatoes with lectin	Taking soda baths, pectin, fermented foods, spirulina, B3, B6, Cayenne, Bio-Lac EFA, raw foods, HCl & Pancreatin Vit. E, Cell food, Celtic Salt Enzymes, Potassium citrate, flax oil, omega 3, niacin, Trace minerals, ozone, chelation, Liquorice root, organic foods eliminate nightshades Alkalai, & Sanavis & Nigerrin Mucolohil & HCl in IV form CBC, Ozone, Blood transfusions, IV Therapies
	Too few E1	Inadequate immune response, radiation, chemotherapy, free radicals	IV Therapies
	Too many E1	Infection, digestive issues, look for doxorubicin, allergies, Hodgkin's Leukaemia	CBC, VH C IV, HCl, pH balance, ↓ stress SCIO, Garlic, Alkalai
	Viability below 75% E2	Bacterial, fungal, viral infections, Chronic fatigue, smoking, hypoxia, low HCl, Vit. C and zinc, increased sugar intake, candida, fungus, digestive insufficiency, increased fructose, (corn syrup) intake	Raw thymus, grapeseed, Vit. C, Ozone therapy & perspiration baths, HCl & pepsi with meals, Glutathione Sanavis, Candida protocol, Lavender oil Super oxide dismutase (SOD) trace minerals, Bio-Lac, Blue Lite
	Parasitized WBCs (Eosinophils) E3	Non steroid drugs, hypoxia of bowel filler fillings, dysbiosis, leaky gut, ALS leukaemia, parasite infection, impaired cellular defense, Hodgkin's more than 1-1% means allergies dark circles under eyes, white spots on finger nails, eczema, fluid retention, Smoking	Rebas, Latenin, Recurcin, SCIO testing for foods, parasites, Spenglersan, Glutathione test for Candida, ↑ Vit. A, C B6, Zinc Utilin 'S' to unblock WBC
	Hypersegmented WBC E4	↓ HCl, B12, folic acid, poor immunity, chemotherapy, chronic deg. Diseases, Malabsorption, glossitis, magenta red tongue, depression, menopausal issues, at risk of heart attack	SOD, mineral analysis for Zinc Copper, manganese, Green Leafy veg, Legumes, spinach, B12, HCl, Glutathione
	Lysing WBC E5	Immune compromise, cortisone use, Lymphatic issue, geopathic stress B12, Folic acid imbalance, dental foci, copper pipes, heavy metals, assimilation and digestion issues	Enzymes, pH balance, see viability above SCIO for heavy metals, Spenglersan Alkalai, Sanavis, Nettle Tea, Bio-Lac

**Mary Kovacs B.Sc. N., 905-562-7159**

## SUMMARY OF POTENTIAL DISEASE FACTORS & RECOMMENDATIONS

according to

Gaston Naessens D.Sc., Prof. Gunter Enderlein, Dr. (Med.) Maria Bleker, Dr. D. Branigan MD,  
Dr. James Privitera MD, & Dr. Konrad Werthmann MD.

for HEALTH MONITORING  
not for DIAGNOSING or CONFIRMING a DIAGNOSIS

AREAS OF OBSERVATION	SIGNIFICANT OBSERVATION	POTENTIAL DISEASE FACTORS	RECOMMENDED ACTION
1. Changes in Outer Wall of RBC	RBC Linkage/Leaky gut B1	Lipoproteins in serum, Leaky Gut ↑ Protein in blood, digestive issues Imbalanced electrolytes, liver stress Hormonal imbalances, Stress, EMF/ELF Radon, ionizing radiation, coffee, cigarettes, toxins, hypoxia Healing crisis, poor circulation Mental & chemical stressors Carbonated caffeine drinks, fructose Refined sugars, meats, hypoglycemia	↓ Protein, ↑ Raw foods, pancreatic enzymes, Protease, Lipase, Lycopene, Monopotassium Phosphate, Calcium Lactate, Valerian Root, B 3, HCl, Potassium citrate or complex Leaky Gut Protocol, Identify stressors Trace minerals, pH balance, Bio-Lac Rebas, Recurcin, Latenin, Mucolohil w/Alkalai,
Word about pH			
	Micro RBC (Microcytes) B2	Please measure urine pH first thing in the morning, Do a midstream sample. <b>NORMAL: 6.50 - 6.80</b>	Pregnancy ↓ in B12, Folic Acid, iron deficiency Osteoporosis, Fatigue, ↓ hemoglobin count Anemia, Migraine, chills
	Macro RBC (Macrocytes) B3	Please measure saliva pH first thing in the morning before you brush your teeth or drink water. <b>NORMAL: 6.50 - 6.75</b>	Pernicious anemia, quick food transit Iron & enzyme deficiency, Lack B12, Folic acid, Vit. A, B & C Food allergies, ↓ Nutrient Absorption Problems with Intestinal flora Increased Endobiosis, parasites, Ileitis/Pancreatitis/high fat in stool Leaky gut, fish tapeworm, stomach Surgery, tumors non functioning bowel Loops, small bowel inflammation
	Oval RBC (Ovalocytes) B4	Junk food, Alcohol, Dilantin, Septa ↓ B12, Folic acid & Iron Endocrine/hormonal imbalances Depression, iron deficiency anemia Pregnancy, PMS, birth control pills Fatigue, dizziness	Stomach/liver duodenum glandular ↑ Folic acid, B12 Brewer's yeast, digestive enzymes Lactobacillus acidophilus, Bio-Lac Fortolehl,
	Various sized RBC (Acanthocytes) B5	Sickle cell & other anemia, Liver dysfunction, energy Iron, Folic acid & B12 deficiency	pH balance, Bio-Lac, Stomach extracts Correct nutritional deficiencies, HCl, Raw green foods, sprouted foods, Kelp Folic acid, B12, iron, CBC, Enzymes
	Ghost RBC (Hemolysis) B6	Indicates presence of antibodies, Parasites, toxins Lipid membrane weakness of RBC Poor assimilation	Blackstrap molasses, enzymes, Bio-Lac Yellow dock root, beet root Iron chelate, Folic acid, raw foods Trace Minerals
	Bottle-capped RBC (Polycytoctes) B7	Free radical activity, Junk foods, fatigue Hydrogenated fats, polluted water Metal, chemical toxicity, sick building Oxidative injury to cells, CFS Radiation & Chemotherapy	SCIO for foods, molds, Glutathione, Balance pH, Detox, Mineral analysis Super Oxide Dismutase, Liver cleanse Zinc, Vit. C, E, Enzymes, HCl, Pancreatin, spleen glandular, Alkalai
	RBC with irregular outer wall and Paroxo-crystalline hump (Acanthocytes) B8	Cirrhosis, hepatitis, Vit. E lack Hypercholesterolemia, ↓ potassium Spleen issues, kidney & liver stress, Infection, Candida, fatigue	B12, Folic Acid, Vit. C, B6, Vit. E Raw duodenum, liver, stomach, Extract, Macro minerals, RTRE, Mucolohil, Sanavis, Alkalai, Candida Protocol
	Broken RBC (Schlaocytes) B9	Free radicals, Food assimilation issues, Plugged hepatic and gall ducts Gall & Liver issues	Blackstrap molasses, enzymes, Bio-Lac Yellow dock root, beet root Iron chelate, Folic acid, raw foods Detox liver, gall bladder

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**Title:**

**THE CHIROLIQUICRYSTAL MICROSCOPE  
TECHNIQUE OF  
FREEZING ANALYSIS OF THE POLYMORPHIC SHAPE  
STRUCTURE OF A HOMEOPATHIC**

**(Freezing as a Technique of Analyzing the Clath Rate  
Structure of a Water-Based Homeopathic)**

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**THE CHIROLIQUICRYSTAL MICROSCOPE TECHNIQUE OF  
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**Abstract:**

Water actually has a liquid crystal phase which seems to imprint memory. This is the basic treatise of homeopathy. Homeopathic medications seem to have the ability to take an imprint from certain pharmacological substances and "remember" some type of shape that is transmitted to shape receptors in the patient's body.

Since water is truly a liquid crystal, this type of water shape memory should be detectable through freezing. In this study homeopathics were frozen at -5° C, at which time an interferometer microscope was used to analyze both the surface and interior crystal lines that formed within the ice.

As freezing takes place, shear lines should develop along the liquid crystal effects of the compounds, and then be discernable using the microscope. This study describes the basic apparatus and technique of analysis and some preliminary results of analyzing various homeopathics. This allows us to ascertain some of the difference in liquid crystal structure of various homeopathic compounds, and also to use this as a quality control technique for developing and producing homeopathics.

**Background:**

The study of homeopathy has led to the study of the clath rate structure of water. The clath rate structure of water accounts for the liquid-crystal effect of water, and the different polygonal structures that water can duplicate in its liquid state.

Elab #1 from PATENT/ELABS. All Elabs will be from that document. 7/6/92 The dipole structure of water forms a 104.5° angle between the two hydrogens with the oxygen as the vertex of the angle. This particular angle allows a water molecule to blend with other water molecules in certain limited fashions. Thus in the structure of water alone with this 104.5° angle water molecules can be added to form different polygonal structures [Studies: 2].

So if we had a model of the H<sub>2</sub>O molecule and we were asked to make a square, given enough molecules, we could do that. We could also make a cube, or a polygon. But there are several structures that we cannot make. Out of the seven great polygonal structures we can only make five with just water. With the addition of alcohol and water we can now duplicate any of the seven, which means that any structure at all that we would want to duplicate could be duplicated with a water/alcohol combination [Books: 10]. If we wanted to duplicate the structure of, for example, DNA, the water and alcohol molecules could be aligned in such a fashion that the shape of the DNA could be imprinted into them, such that the water and alcohol molecules could produce a very similar shape.end elab #1

With the addition of alcohol other structures can be duplicated; therefore, the need for the water and alcohol mixture used in homeopathic pharmaceutical preparation. What this means is that as we take different herbs, sarcoes, nosodes, allersodes, isodes, etc.; and potentiate them through serial dilution and succussion, there is an imprint of this item into the liquid crystal of the water and alcohol.

Liquid crystals were discovered in 1888 by an Austrian botanist named Frederick Reinitzer. He was studying the effects of cholesterol in plants. Cholesterol mystriate and other cholesterol compounds are among the best liquid crystals. Vorlander studied liquid crystals further, and today the Martin Luthor University in Halle still boasts an important liquid crystal institute, which has been there since 1900.

Much of the work on liquid crystals has led to the development of the liquid crystal display used on many computers and watches. Without the analysis of how some liquids can join to crystals, these electronic discoveries could not have been made. Most of the work on liquid crystals has been done on the larger compounds in the cholesterol range, and also in some of the electronic areas. However, it is known in the industry that water can also form a liquid crystal.

Liquid crystals do not often have the propositional organization that solid crystals bost, but they do have organizational or vectoral componentrs which allow them to maintain a type of phas space dimension, or a shape memory.

In the book "Liquid Crystals" {Books: 11}, Peter Collings reports that in 1988, seven hundred scientists from thirty-one countries gathered in Germany for the twelfth international liquid crystal conference. They fully attested to the science of liquid crystal analysis.

In analyzing the liquid crystal effects of water, researchers in France in the 1970s found that when certain waters were frozen had a specific type of crystallization effect which seemed to orient itself along magnetic pole lines and develop certain crystalline structures. When the water was thawed and refrozen, these structures would remain. In fact, the researchers found that the only way to destroy these structures in the water's memory was to heat the water to the boiling point. Somewhere between room temperature and the boiling point there seems to be a heat threshold which would destroy the water's memory.

Our research has found that this threshold is at 60° C., or approximately 140° F. Temperatures higher than this threshold seem to be able to so increase the Brownian motion and thermal agitation of the water that it would lose its memory effect. Thus this would be a temperature that would destroy the communication ability of homeopathy.

In 1988 an importer of homeopathic medicines in America had a malfunctioning airconditioning unit in their warehouse. This happened during an

exceedingly hot period in California. This researcher was asked to check with the chiroliquicrystal microscope technique and the RAEGE unit [Studies: 3] to determine whether any of the homeopathics had lost their potency or organization effects. One skid was identified as being destroyed because of the excess temperatures. This was the skid of homeopathics that was in the corner and endured the most heat.

Researchers in France studied the memory effect of water, and found that it also could be destroyed if the water was passed through a small enough nozzle. Small enough injection needles would also interfere with the ability of the homeopathic to remember its various shapes.

Thus from our research on ultra-high dilution homeopathy (potencies beyond 30x) we know that there is no original chemical left; yet the homeopathic seems to have an ability to transfer some information. One process is in the liquid crystal memory effect of water.

Elab #2 7/6/92 In the 1960s and '70s at the Hahnemanian Hospital in Philadelphia, Pennsylvania, studies of nuclear magnetic resonance effects of homeopathy were undergone. These studies proved that homeopathy could transfer a magnetic resonance shape into an alcohol and water mixture. In doing this study they took a normal water and alcohol mixture that was not homeopathically succussed and tested its magnetic resonance. It was found that the magnetic resonance effect was random in the positioning of the water molecules. When they took different homeopathics that were succussed to 30x and beyond, so that there was no original in them, they found that when the water and alcohol underwent nuclear magnetic resonance, it did not produce random tracings. They did, however, produce significant consistent results, perhaps reconfirming our hypothesis that water and alcohol can hold the shape of a substance through succussion.end elab #2

This polymorphic shape transfer of the homeopathic into the body can be accomplished through the shape receptors of the nasopharynx area and the olfactory nerves and taste buds, as well as the shape receptors on cells throughout the body.

Elab #3 7/6/92 The chemicals within an herb, such as the ergine alkaloids of Belladonna, have a specific structure and crystalline set of angles and shapes that determine their effects. Thus the structure of the Belladonna is important, as it activates different shape receptors within the body. The shape receptors of the nasal pharynx (the number-one place for shape receptors in the body) can be stimulated if the shape is contained in a water and alcohol mixture. This accounts for the polymorphic structure of homeopathy beyond 30x.

In the studies of Beneviste he found that items beyond 23x and 30x were still able to stimulate antigen release in blood cells. If we look at the antigen factors with the idea of a transfer of shape via the shape receptors of the white blood cell, we can see that perhaps Beneviste was indeed correct in his work. He found that the 30x of an antigen, such as milk, could produce an antigenic reaction in his substances. One possible way to explain this would be that the milk in the succussion process had imprinted its shape into the water and alcohol molecules of the homeopathic preparation. Homeopathy works by triggering the shape receptors on the white blood cell (this is how the IGG, IGM, IGE, IGA, and the entire immunoglobulin process, works on shape receptors). Thus a compound shape could be imprinted into the water and alcohol, and act on the shape receptors of a cell in the body.

The structure could be imparted by an herb into a water and alcohol

combination.end elab #3

Thus the homeopathic preparation imparts into the liquid-crystal structure of the water and alcohol some shape that can then be transferred through the shape receptors into the body for recognition of the energy of this shape. Then the body can respond in a medicinal fashion.

This phenomenon of shape transfer has been difficult to study because of the lack of the proper mechanism. The purpose of this study is to develop such a mechanism for study of the polymorphic shape of the liquid-crystalline structure of homeopathic pharmaceuticals.

Elab #4 7/6/92 Thus a compound such as Belladonna, which has an anti-cholinergic effect, makes the body red as a beat, dry as a bone, and mad as a hatter. This is the biochemical effect of the atropine in the Belladonna compound. When we use a homeopathic solution of this, we succus the Belladonna compound so that the same structure can be imprinted into the water and alcohol substance.

Thus the water and alcohol reproduce the actual structure of the atropinous compounds in the Belladonna as well as all the other compounds. In the compound of Belladonna the atropinous molecules are the most pharmacologically active. When the shape comes into the body of the atropinous compound, it can trigger shape receptors in the body. The shape receptors in the nasal pharynx area, one triggered by the shape of atropine, can prepare for the presence of atropine. Thus the brain, having been alerted by the shape receptors that atropinous Belladonna is on its way into the digestive tract, might turn on its anti-redness, anti-dryness, and anti-madness device.

This could account for many reversible symptoms in homeopathy. This happens through the Arndt-Schultz law of poisons. This is accounted in *Natural Repertory* of Dr. Nelson.

In the case of a more inane substance we might site a compound such as Thymusin. Thymusin is a hormone released by the thymus gland that helps to stimulate white blood cells. In the presence of its shape the brain might secrete more Thymusin or help stabilize its Thymusin regulatory circuitry.

Thus we can see the need to study the polymorphic structure of water and alcohol in homeopathics. This is just one way that potential information from a biological substance might be pushed into a water and alcohol mixture. This helps to account for the field of homeopathy.end elab #4

To study the shape we need to freeze the homeopathic pharmaceutical, which will cause crystalline freeze boundaries to develop along the lines of the crystalline structure of the liquid as it develops into a solid. This can be easily accomplished by taking the homeopathic pharmaceutical and freezing it at -5° to -10° C., using low alcohol in the five percent range. This freezing will cause a reflection of the crystalline structure to be accomplished in the crystalline lines that will appear within the freezed mixture.

Elab #5 7/6/92 In the nuclear magnetic resonance studies done at the Hahnemanian Homeopathic Hospital, they found that there was indeed a shape that could be imparted into water and alcohol. Their nuclear magnetics work did not allow them to discern what the shape was, but they could tell that there was a consistency of shape. They also found that the consistency of shape needed at least 5% alcohol solution, or 5% water. Somewhere between a 5% alcohol solution and a 95% alcohol solution homeopathics were able to function.end elab #5

Elab #6 7/6/92 Thus the freezing of this homeopathic will allow us to see

some of the shapes that will develop along the sheer lines in the water and alcohol. Since the shapes will be quite small, we will have to account for the crystalline structure of these sheer lines to be projected outward. We will need some mathematical analyses to determine the shape of the water and alcohol mixture. But first we need to look at the actual device utilized in this test.end elab #6

## Instrumentation:

The mechanism needed for analysis will then be a microscope with polarization capacities that will need its specimen tray kept cold; hence the need for the cyroliquicrystal microscope. This microscope will need a cold chamber where the frozen homeopathic preparation will rest, allowing for light to filter through the cold chamber. This filters out some of the infrared rays, so that the light used for analysis will not melt the lines we wish to investigate. This microscope will also need polarized light filters to allow us to change and investigate the effects of polarized light on the liquid-crystal structures. The power of the microscope need only be in the range of 100x through 500x. The diagram in Figure 1 shows this microscope fully.

The microscope itself will sit inside a polystyrene plastic box. The plastic box will be air-tight, and have a door on one side to allow us to put a new slide or specimen into the microscope area, and also to be able to clean any part of the microscope. Once closed the door will create a closed area which can be refrigerated by an external-mount refrigerator. The thermostats mounted inside the specimen box will keep the air within that box at a temperature of approximately -5° C. The air circulating into the box will also need to be run through a dehumidifier, so that fogging and crystallization will be kept to a minimum on the lens surfaces.

The light source for the machine will be external mount, and carried through mirrors and infrared filters that will filter most heat or types of electromagnetic radiation out of the light and allow for a polarization effect on the specimen. The polarization filters will be purchased from the Polaroid Corporation. The polarization filters also will need to be rotated for proper polarization.

The barrel of the microscope will stick out of the box and allow for comfort in viewing the specimen while it is maintained at a low temperature.

The homeopathic pharmaceutical preparations are diluted one part to ten, one part to one hundred, or one part to one thousand; the serial dilution imparts some degree of information into the formula, because once we pass 25x to 26x we go beyond Avogadro's number in the limitations of the amount of mass that could be in the dilution. Yet, homeopathy continues past 30x, 60x, 100x, even 1000x range; partially because of the transfer of the shape into the liquid crystal of water through its clathrate structure. Then this shape information is transferred into the body by the shape receptors in the cellular structure of the organism.

This phenomenon of shape transfer has been accounted in the works of William Nelson, in *Natural Repertory*, as well as quality control for homeopathy.

It is the purpose of the Cyroliquicrystal Microscope one must only use any typical low-range microscope. The microscope should then be equipped with simple polarizing filters such as Kodak polarity filters. Then around the view

table a cold box is constructed of clear plastic, approximately 5" x 5". This cube needs a front door to take specimens in and out of the cold box. In the back of the cold box, out of view, two ports are placed; one intake and one out-take. These are connected to a typical refrigeration unit such as Kodak polarity filters. This refrigeration unit will circulate the cold air through the cold box. This will maintain the needed -5° C. to keep the homeopathic liquid frozen while viewing, the homeopathic liquid is frozen in a 2 cm. circular dish 1 mm. deep. This freezing follows the liquid crystal patterns of the polymorphic structure of the homeopathic.

### Results:

The Cyroliquicrystal microscope is for quality control of homeopathic pharmaceuticals. It is designed to detect the patterns of homeopathics in the water and alcohol preparations. These patterns in the liquid crystal of the water will be insightful in homeopathic quality control.

Bill's diagram of the telescope goes here. 7/6/92 In analyzing thousands of homeopathics for their shape structures, we have seen that the chiroliquicrystal microscope allows us to see the organizational structures of the clath rate vectoral components of the water. Freezing does not affect homeopathy; when a frozen homeopathic is thawed, it returns to its original shape. We do find that the thermal agitation of heating has a destructive effect on the homeopathic.

We also can see that the process of making an ultra-high dilution homeopathic is very tentative, as the liquid crystal effect of water is also very tenuous, and often unstable. It was found that in the normal process of manufacturing homeopathics with normal water and alcohol, there was approximately a sixty-five percent chance of the final ultra-high diluted product in the 30x range to maintain its communicative shape. In other words, only sixty-five percent of the homeopathics analyzed were able to reveal similarities in the crystalline structure.

When the homeopathic patented water process of Dr. Nelson was used, there was an increase in the success rate [Patents: 1]. This process allowed for the development of an electrical activation of the water which increased the zeta effect, and thereby theoretically should allow for a greater ability of the polymorphic structure of water and the liquid crystal effect of water to imprint the shape. There was then an over ten-percent increase in the consistency of the homeopathics from the utilization of the patented water.

Thus we can see how it is statistically improbable for homeopathy that is manufactured without strict quality control standards to maintain this polymorphic structure when the water and alcohol molecules are succussed past 30x.

Homeopathy thus offers a dramatic ability for society in that it offers a safe, and yet effective, form of medicine. The action of homeopathy on the shape receptors in the nasal pharynx would definitely explain much of the phenomena of homeopathy, in that a poison or nosode would trigger shape receptors to then activate processes in the brain that would prepare for the intrusion of the poison or nosode. A sarcode, however, might alert the brain to help to stabilize processes. An allersode could be used for desensitization, and an isode could be used for reversal effect. Thus much of homeopathy can be understood in this polymorphic shape structure.

We also know that Hahnemann first started offering his homeopathics by putting the compounds onto balls of cotton and letting his patients inhale the fumes. Putting the cotton balls under the noses of his patients, he was able to trigger the shape receptors. This was the first form of homeopathy. Later this shifted to liquids, and later still to pills for convenience.

We can see why strong odors would block homeopathy; they would occupy and fill the shape receptors, prohibiting the administration of the shape of the liquid crystal water and alcohol into the shape receptors. Thus our polymorphic structure theory fits into clinical experience as well.

Ongoing work has been done in homeopathy on the confirmational compounds of the hydrogen bonding effects [Studies: 4, 5]. These studies reveal that homeopathics also have the ability to enhance and affect the hydrogen bonding effects of water. This allows us to understand some conformational binding effects, which allows for a better understanding of the liquid crystal dynamics.

The work done by Olga Zhalki-Titarenko also was significant in showing how the homeopathic patented water had an increased organizational effect on the conformational hydrogen bonding proposition for the homeopathic. Homeopathics made with the patented process have a superior organizational structure as determined by the hydrogen bonding and magnetic resonance machinery.

In understanding the liquid crystal effect of a homeopathic, we can also see how heating the homeopathic with high temperatures is destructive through thermal agitation. Thus homeopathics exposed to radiation and high temperature have their organizational material challenged, and possibly disrupted. This can also be measured through the chryroliquicrystal microscope, the REGAE equipment, the hydrogen bonding effect, and the like. Companies that sell the most homeopathic injectables may wish to reconsider this method, and have their homeopathics analyzed for quality control by our processes, in that all of their injectable homeopathic vials are exposed to temperatures past 160° F. This is for sterilization purposes, which are good for controlling cultures, but which are bad for organizational liquid crystals.

It was found in our research that this is a prohibitive means of treating homeopathics, as it destroys some of their informational context. The lower-potency items (below 12x) are often not destroyed by this technique, although some are. It is the high-energy forms of the homeopathics that are most often destroyed at the higher temperatures.

Another challenging and disturbing component of this research is that the lactose pills or the milk sugar are very poor liquid crystal media, and do not have the specific ability of memory that the water and alcohol have. Thus some homeopathic lactose pills also can be demonstrated to have a low ability to produce the polymorphic shape structure communication that has been superbly determined in the water and alcohol medium of homeopathy.

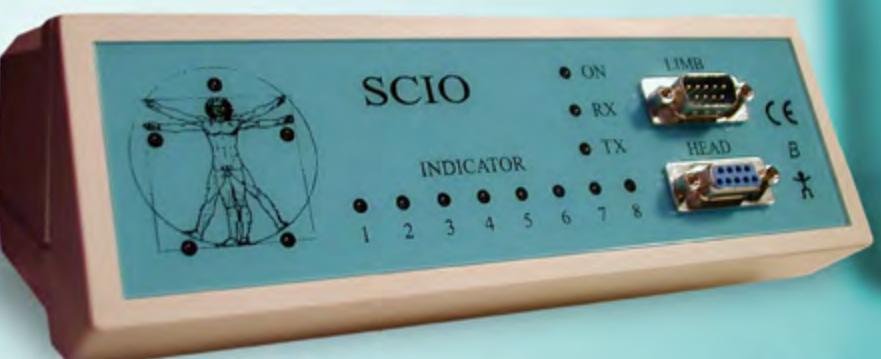
### Conclusion:

In conclusion, homeopathy as a profession that is moving increasingly into quality control in scientific and statistical analyses must meet some very stiff criteria and deal with some issues that challenge some of the age-old dictums of homeopathy

which might have led to modern medicine's classification of homeopathy as placebo. Perhaps much of it actually *is*. Much of homeopathy is still being made with lactose pills at ultra-high dilutions in which there seems to be no documentable evidence of the transfer of the energy effect of the homeopathic.

In the water and alcohol medium of homeopathy there plainly appears to be a process in which the liquid crystal effect and the polymorphic shape structure seem to trigger various shape receptors.

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Figs. from pgs 88, 90 & 92 of QQC book here..



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## ARTICLES AND STUDIES

**THE CHIROLIQUICRYSTAL MICROSCOPE TECHNIQUE OF  
FREEZING ANALYSIS OF THE POLYMORPHIC SHAPE  
STRUCTURE OF A HOMEOPATHIC  
(Freezing as a Technique of Analyzing the Clath Rate  
Structure of a Water-Based Homeopathic)**

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5. **The Influence of an External Electric Field on the Structure of Water and Solvation Spheres of Bio-Ions and Biomacromolecules (Hydrogen Bonding Groups in Homeopathy).** Olga Zhalki-Titarenko; Ukraine Institute, Kiev. 1994.
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This has Darkfield  
stuff in it.

## The Marshall Protocol for Lyme Disease and Other Chronic Inflammatory Conditions

### Part Two: Scientific Background, Data, and Case Histories

by J.C. Waterhouse, PhD

#### Introduction

Part One of this article focused on how to apply the Marshall Protocol (MP) to chronic Lyme disease (a.k.a. post-treatment Lyme disease syndrome) and a variety of other chronic conditions.<sup>1-5</sup> Part Two will discuss the scientific background in more detail after first presenting data and case histories illustrating the effectiveness of the MP in treating a wide range of inflammatory diseases, including diseases associated with aging.

All the conditions responding to the MP appear to have a similar causation by treatment-resistant cell wall deficient bacteria (CWDB) (see Sidebar). The protocol involves immune modulation, which consists of vitamin D reduction and higher than usual dosages of the angiotensin II receptor blocker, olmesartan (Benicar). These two components of the protocol enable the immune system to kill the CWDB weakened by the third component of the MP, namely, very low dosages of certain antibiotics.<sup>1-3</sup>

#### Role of CWDB and Other Treatment Resistant Bacteria: Evidence

1. Decades of research on difficult-to-cultivate bacteria using different names: cell wall deficient bacteria, L-forms, cysts, filterable forms of bacteria, mollicutes, Russell bodies.<sup>4</sup>
2. Photographic evidence of CWDB and bacterial life cycles in Lyme disease, rheumatoid arthritis, uveitis, sarcoidosis, Alzheimer's disease, Parkinson's disease, etc...<sup>2,3</sup>
3. More recently, treatment-resistant bacterial forms termed nanobacteria, persisters, dormant forms, and biofilms are being studied.<sup>10,11</sup>
4. Failure of past antibiotic regimens to eradicate these bacteria leads to doubts of their importance.<sup>7</sup> This failure appears to be remedied by the Marshall Protocol.<sup>1-3</sup>

#### Early Results from Ongoing Phase Two Trial

##### Data

Preliminary results for chronic Lyme disease patients show that of the 51 patients who have been followed on the protocol study site for six to 22 months, 29 are reporting tangible improvement (Reenie Gentile, written communication, July 25, 2006).<sup>2</sup> Marshall<sup>4</sup> also finds significant improvement rates in various other chronic diseases (Table 1). These results probably underestimate the ultimate efficacy of the treatment, because many patients were still in fairly early stages of treatment and were still undergoing strong immunopathology responses to bacterial killing (a.k.a. Jarisch Herxheimer Reactions<sup>1-3</sup>).

##### Brief Case Histories

The following are brief case histories. (For additional information, please visit [http://autoimmunityresearch.org/transcripts/recovery\\_lax2006.pdf](http://autoimmunityresearch.org/transcripts/recovery_lax2006.pdf); also see Table 1 for patient improvement rates in other chronic diseases.)

Patient 1 is a 14-year-old boy who has been ill with chronic Lyme disease (with Rickettsial and Chlamydial coinfections) since June 2004. He suffered from chronic severe headaches, debilitating fatigue, a Tourette-like tic occurring every few minutes, blurred/double vision, photophobia, nausea, vertigo, insomnia, and visual tracking problems that prevented him from reading or writing. After 16 months on the MP, all his symptoms have greatly improved, and his tic and visual problems have completely disappeared. He is now able to resume most of his previous activities and continues to improve on the protocol.

Patient 2 is a 58-year-old woman who was diagnosed with Lyme disease in 1999. She had been treated with oral doxycycline in 1999 and 2001. She relapsed after beginning the MP. She has had 70-75% resolution of brain fog, fatigue, and lymph node swelling. She still requires injections of IgG due to a deficiency of IgG3, but the injection interval has increased from an average of 14 days to more than 24 days since commencing the MP. After 22 months on the protocol, she reports feeling markedly better than anytime in the last 20 years and is able to work full time and perform strenuous physical activity.

Patient 3 is a 55-year-old female who was diagnosed with rheumatoid arthritis ten years ago. She had previously been on high dose antibiotics (mostly oral, with some IV and IM) for six years prior to the MP and had minimal improvement. Her condition worsened while taking vitamin D prior to the MP (800 to 2400 IU daily over a two-year period). After 29 months on the MP, she reports reduced pain medication use, significantly greater strength and less pain in her hands and upper body, and less fatigue. Recently, her anti-nuclear antibody (ANA)

tested negative, after having all 17 prior tests showing elevated levels (usually 1:640 or more).

Patient 4 is a 42-year-old man diagnosed with chronic fatigue syndrome and fibromyalgia. His illness began after he became ill with infectious mononucleosis at the age of 22. Prior to beginning the MP, he could only work two or three days per week and had adverse consequences for days following exercise. He began the MP in March of 2005, and since then, he has had 90-100% resolution of his headaches, light sensitivity, tinnitus, sinus congestion, sore throat, unrefreshing sleep, swelling of fingers and feet, fibromyalgia, and heart palpitations. He has had 70-75% resolution of brain fog, fatigue, and lymph node swelling. He still requires injections of IgG due to a deficiency of IgG3, but the injection interval has increased from an average of 14 days to more than 24 days since commencing the MP. After 22 months on the protocol, he reports feeling markedly better than anytime in the last 20 years and is able to work full time and perform strenuous physical activity.

Patient 5 is a 43-year-old man who had psoriasis since the age of seven, chronic insomnia beginning at the age of 26, and sarcoidosis, diagnosed at the age of 36. His wife had been diagnosed with sarcoidosis several years before. This is in accord with the familial tendency that has been observed among Th1 diseases due

to spread of the bacteria among family members. Prior to the MP, numerous treatments had failed to help his psoriasis (e.g., PUVA, steroids, fish liver oil). In contrast, while on the MP, the psoriasis went from 70% coverage of his skin to one percent. The insomnia resolved completely soon after the Benicar was begun. The patient had also suffered from chronic kidney stones, which ceased when he began the protocol. Treatment with the MP has resulted in more than 95% resolution of his symptoms of sarcoidosis (coughing, fatigue, sinusitis, memory problems, muscle aches, etc.). and his chest X-ray is now normal as he continues his fourth year of the MP.

Patient 6 is a 48-year-old woman who was diagnosed with sarcoidosis in 1991. In 1998, she developed seasonal affective disorder (SAD) and began taking anti-depressants every winter to treat the depression. After beginning the MP in October of 2006, she found she was not depressed and did not need her anti-depressant. The combination of taking 40 mg Benicar every six hours and avoiding vitamin D was sufficient to relieve her SAD (she wears a zinc oxide that contains sunscreen to help minimize vitamin D production and NoIR sunglasses). She has only been on the MP for a few months, but finds her fatigue has significantly lessened.

Patient 7 is a 61-year-old woman with presumed sarcoidosis (based on CT scan), with unilateral tibial

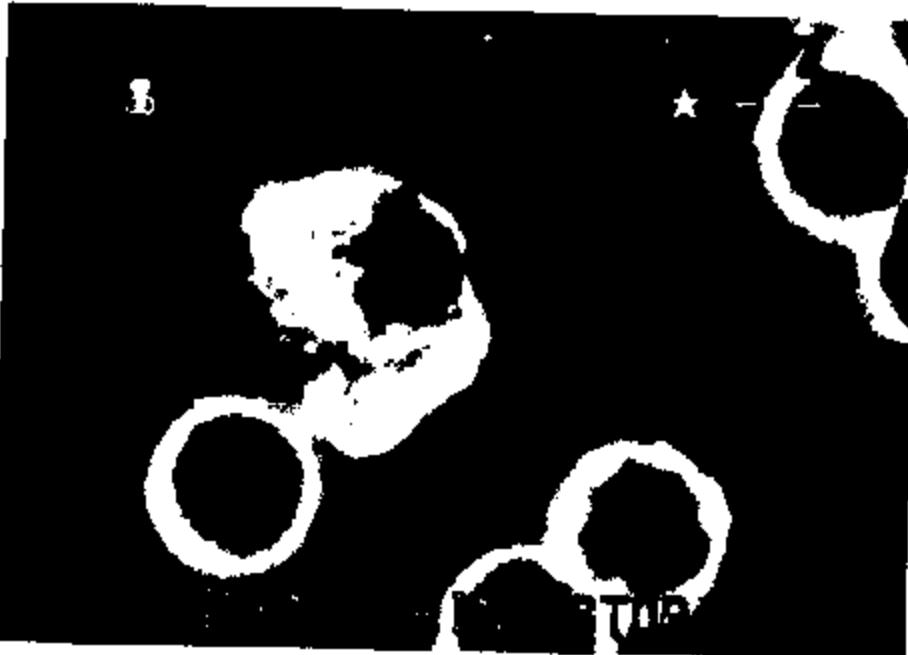
Table 1: Improvement Rates In Other Chronic Diseases

	Number of Patients/Numbers Reporting Improvement
Rheumatoid Arthritis	8 / 7
Hashimoto's Thyroiditis	25 / 20
Osteoarthritis	5 / 4
Chronic Fatigue Syndrome CFS/ME	77 / 40
Cardiac Arrhythmia	15 / 9
Sarcoidosis	92 / 57
Type 2 Diabetes	5 / 3
Uveitis	18 / 12
Fibromyalgia	34 / 20
Irritable Bowel Syndrome	10 / 8

## Marshall Protocol

neuropathy presenting with altered sensation, severe foot atrophy, and calf muscle cramps. So far on the MP, she has regained 95% of her muscle tone, strength, and mobility in her foot and leg. Her fatigue, depression, and cutaneous lesions also resolved. Two other examples of severe neurosarcoidosis showing marked improvement on the MP are described elsewhere.<sup>3</sup>

Patient 8 is a 67-year-old man who has had sarcoidosis of multiple organs, including the heart and lungs, for over 20 years. He had a pacemaker implanted in 1995 and has undergone two quadruple bypasses. He had been in atrial fibrillation over 90% of the time in



This photograph shows a dying white blood cell from which cell wall deficient bacteria (CWDB), in the form of fine biofilm filaments, appear to be escaping. Biofilm filaments are composed of CWDB and a protective protein sheath. The other cells in this photo are red blood cells.

CWDB (a.k.a., L-forms or cysts) take on many different forms that often allow them to escape destruction by the immune system and/or antibiotics. However, the Marshall Protocol is able to circumvent their resistance mechanisms and successfully treat chronic inflammatory diseases, including Lyme disease, through a specific type of immune modulation combined with very low doses of carefully chosen pulsed antibiotics.

Early photography of CWDB originated nearly a century ago and was continued by the Wirostko, et al., Cantwell, Mattman, and others (3, 5, 6 and <http://autoimmunityresearch.org/borrelia-survivalunderadverseseconditions.pdf>). The extensive photographic record reveals bacteria inside the cytoplasm of cells, as well as in various forms outside of the cells. (Photograph courtesy, Andrew Wright, MD, UK).

the two years prior to the MP. After three months of treatment with the MP, with no other changes in medication, his atrial fibrillation disappeared and has not returned in the following 20 months. His chest X-rays have improved significantly, and his shortness of breath and fatigue have also improved as he continues on the MP.

Patient 9 is a 51-year-old woman who has been diagnosed with numerous conditions over many years of being ill. Since beginning the Marshall Protocol, her symptoms of Lyme disease (muscle/joint pain, fatigue, cognitive problems) and her Sjogren's syndrome and Raynaud's symptoms have significantly improved. Her myasthenia gravis, diabetes insipidus, gastroesophageal reflux

disease, Barrett's esophagus, interstitial cystitis, allergies, multiple chemical sensitivity, and migraines have greatly improved, and her chronic yeast infections (vaginal and esophageal) have completely resolved. She can now read, use the computer, drive a car, and walk without a cane, things she could not do before the MP.

### Scientific Background of the Marshall Protocol

#### Th1 Disease: Interferon-Gamma and Vitamin D Metabolites

Before going into more depth on the scientific background of each component of the MP, a brief discussion of Th1 inflammation is needed. In Part One,<sup>1</sup> an overview of vitamin D metabolites in relation to the Marshall Protocol was given. Sarcoidosis was presented as the prototype Th1 illness, in which infected macrophages convert the precursor form of vitamin D (25D) to the active, hormonal form (1,25D) at a high rate.

The T-helper Type 1 (Th1) immune response is usually defined as one that generates significant quantities of the proinflammatory cytokine, Interferon-gamma.<sup>12</sup> Many chronic diseases are associated with Th1 inflammation.<sup>12</sup> A high level of generation of Interferon-gamma (IFN-gamma) can result in an increase in conversion of 25D to 1,25D by activated macrophages by as much as 30-fold<sup>13</sup> and a failure of mechanisms that help regulate 1,25D.<sup>14,15</sup> Since 25D and 1,25D circulate in the serum and IFN-gamma does not, these vitamin D metabolites can provide a more useful indicator of Th1 inflammation than serum IFN-gamma.<sup>14,15</sup>

#### Vitamin D and Its Role as a Steroidal Immuno-suppressant

A number of chronic diseases have appeared to improve in the short term when large dosages of vitamin D are given.<sup>17</sup> If the active hormonal form, 1,25D, is tightly regulated, one might wonder how raising its inactive 25D precursor to high levels could have any effect? Molecular modeling results may provide an answer to this question.

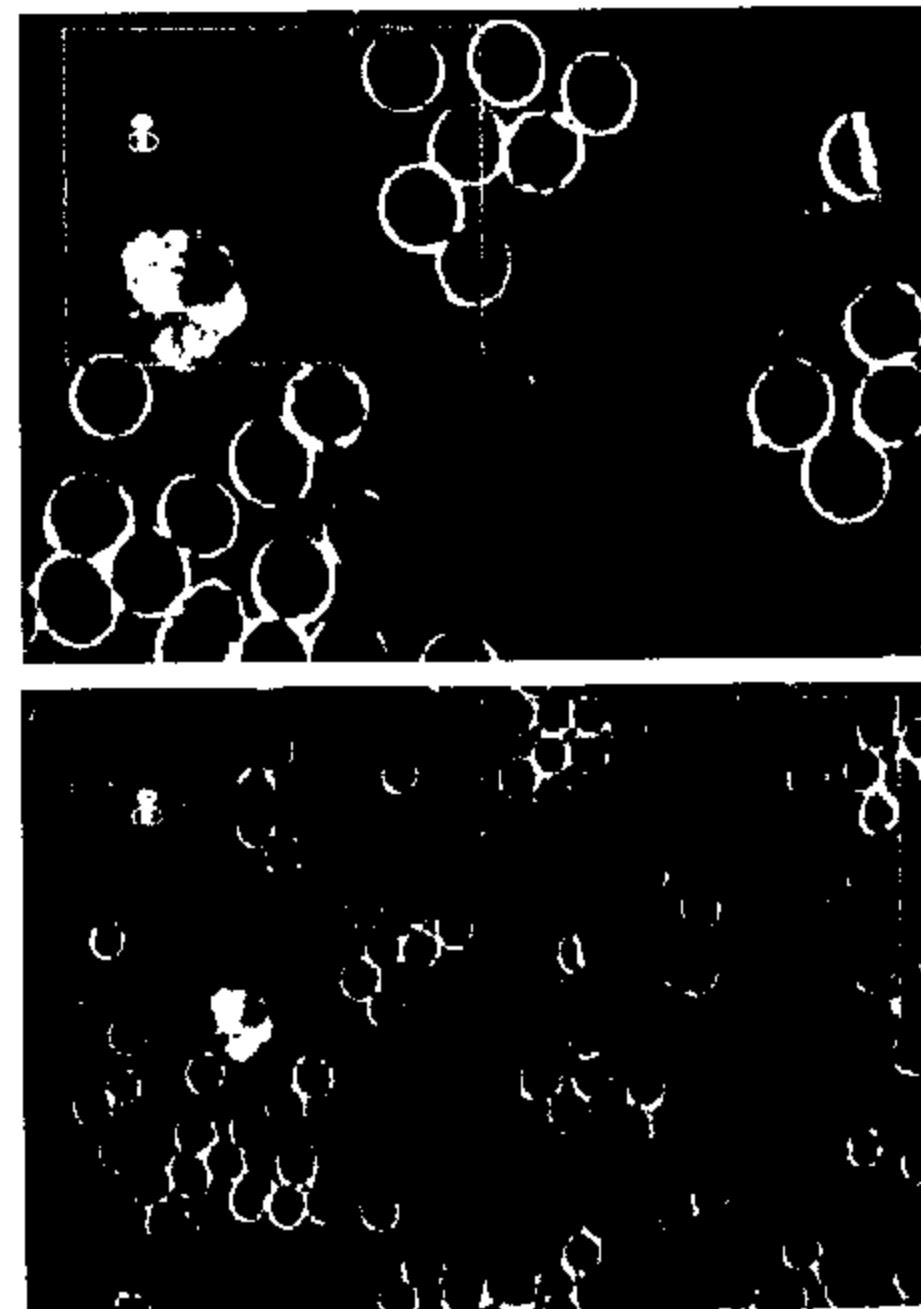
Highly sophisticated computer models of the various vitamin D metabolites and the vitamin D receptor (VDR) show that only the

1,25D form is able to activate the VDR.<sup>4,5,12,13,20</sup> The affinity constants calculated show that other forms of vitamin D, including 25D, can bind to the VDR but do not activate it. These results indicate that above a certain level (approximately 20-25 ng/ml), 25D binds to the VDR and blocks receptor activation.

Blocking of the VDR has important consequences for innate immunity, the branch of the immune system that eliminates intracellular

## Marshall Protocol

organisms. The VDR plays an important role in controlling certain toll-like receptors (TLR2 and TLR4), defensins, and other components of immune function used to detect and kill pathogens.<sup>5</sup> Thus, blocking the VDR with high doses of 25D suppresses the killing of CWDB and other intracellular pathogens.



These photographs are lower magnifications of the photograph on page 87 and illustrate the length of the biofilm filaments and show how strong and cohesive they are.

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The various forms of vitamin D are all secosteroids, closely related to steroids, and the molecular modeling results show that they have a high affinity for various steroid nuclear receptors.<sup>12,13</sup> In fact, at high enough levels, all the major vitamin D metabolites, including 1,25D, can also bind to the glucocorticoid receptor, alpha 2 thyroid receptor, and sex hormone receptors.<sup>12,20</sup> This can account for the hormonal and neurological changes that often occur when vitamin D metabolites become too high or when they are suddenly reduced by the MP.<sup>12</sup> It can also account for the well-known ability of 1,25D to suppress the adaptive immune system.<sup>14,15</sup> By binding to the glucocorticoid receptor, high 1,25D levels appear to be able to act in a manner similar to

immunosuppressive drugs, such as prednisone.

To summarize, recent evidence indicates that high 25D suppresses innate immunity and high 1,25D suppresses adaptive immunity. It follows that high doses of vitamin D may sometimes produce short term anti-inflammatory effects but cause long-term pathogen increases. Conversely, lowering elevated levels of vitamin D as part of the MP is thought to be crucial to the elimination of persistent pathogens causing Th1 disease.<sup>12</sup>

### Vitamin D and the Marshall Protocol: Osteoporosis, Inflammation, Cancer Risk

During the MP, vitamin D levels are modulated through restriction of ingested vitamin D and sun exposure.<sup>21</sup> Levels are kept in the range that generally maintains bone health, if one consumes adequate calcium. By reducing an

elevated 1,25D hormone level, one is better able to maintain bone density, especially near areas of inflammation, where bone loss is more likely.<sup>14,15</sup> Too high a level of 1,25D has been shown to have negative effects on bone density in rheumatoid arthritis and inflammatory bowel disease,<sup>14,15</sup> and a high 25D (>33 ng/ml) has even been found to be a risk factor for prostate cancer.<sup>13,18</sup>

The new view of the role of vitamin D in chronic disease discussed above has required a new interpretation of previous studies on its role in osteoporosis and its relation to secondary hyperparathyroidism, as well as on what is a desirable level of serum 25D.<sup>12,13,15</sup> According to this new interpretation, certain recent assumptions regarding the optimal level of vitamin D have been erroneous.<sup>12</sup> The levels of inflammation and several other

hormones, in addition to 1,25D, are seen as key factors in determining bone density.<sup>5,21</sup>

### Benicar: An Angiotensin Receptor Blocker

One of the most important immune system effects of angiotensin receptor blockers (ARBs) is their ability to reduce excessive levels of nuclear factor kappa beta through blocking the angiotensin II receptor, thus reducing inflammation and oxidative stress associated with elevated IFN-gamma and TNF alpha.<sup>22,23</sup> Molecular modeling results<sup>5,12,13</sup> show that ARBs are also capable of activating the VDR and thus can produce all the various immune-enhancing effects that the VDR stimulates (see above). When 25D is too high and is blocking the VDR, Benicar is thought to be able to displace it to some extent and thus activate innate immunity.<sup>12</sup>

Benicar also binds to PPARgamma, which affects the function of phagocytic cells and CCR2b, which recruits monocytes to the site of inflammatory immune challenge.<sup>12</sup> Other ARBs bind to these receptors as well, but in some cases, they bind to certain receptors with too high an affinity.<sup>12</sup> Experience with the MP has shown that of all the ARBs, Benicar is the most effective for the purposes of the MP.<sup>12</sup>

Benicar was generally well-tolerated in safety evaluations, and has few contraindications.<sup>1</sup> Examples of some of the documented protective effects of ARBs include the ability to do the following: 1. prevent migraines,<sup>24</sup> 2. inhibit liver fibrosis and aid liver healing,<sup>25</sup> 3. protect the kidneys in diabetic nephropathy,<sup>26</sup> 4. reduce insulin resistance,<sup>27</sup> 5. protect the heart from damage from inflammation in myocarditis,<sup>28</sup> and 6. protect the mitochondria from age-associated damage from oxidation.<sup>29</sup> In addition, it has been proposed that angiotensin receptor blockers may also have a direct

antibacterial effect in addition to their immunomodulatory role.<sup>20</sup>

### The MP Antibiotics - Mechanisms of Action

It has been found that patients with Th1 diseases have a wide variety of bacteria contributing to their illness.<sup>3</sup> Used in particular combinations, the MP antibiotics were chosen to work together to target a very wide spectrum of bacteria while minimizing the risk of human toxicity. These antibiotics block protein synthesis, preventing the bacteria from reproducing and reducing their defenses against immune system attack.<sup>3</sup>

Minocycline is used due to its superior lipid solubility, central nervous system and cellular penetration, and broad spectrum ability.<sup>25</sup> Minocycline acts primarily by inhibiting bacterial protein synthesis by binding to the 30S ribosomal sub-unit.<sup>25</sup> Azithromycin is synergistic with minocycline in that it binds two molecules in the 50S subunit of the ribosome. An important characteristic of this unique antibiotic is its superior tissue penetration<sup>22</sup> and the long period of time in which it remains in the tissues. A different

## Marshall Protocol

region of the 50S ribosome is blocked by clindamycin. Bactrim (trimethoprim/sulfamethoxazole) acts by inhibiting the enzyme dihydrofolate reductase. Experience has shown that these antibiotics are far more effective when used with the immune modulation of the MP (10 mg of Benicar every six or eight hours and vitamin D reduction) than when used apart from it (see Caution below).<sup>12</sup>

### Future Developments - FDA Designation and Phase 3 Trials

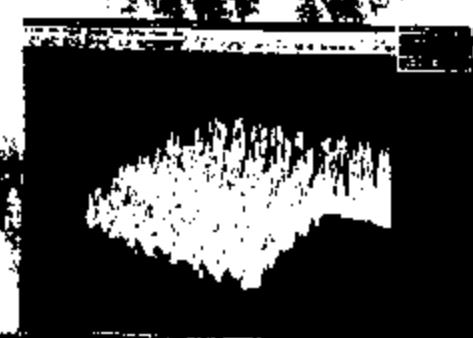
The Autoimmunity Research Foundation has obtained Office of Orphan Product Development, Food and Drug Administration (OOPD FDA) designation for minocycline and clindamycin for treating sarcoidosis, paving the way for phase three clinical trials.<sup>4</sup> Application for OOPD status for post-treatment Lyme disease syndrome (PTLDS) is still pending.

In the future, this new protocol may be applied to many more common diseases. For example,

**Caution Regarding Implementation: The power of these antibiotics is so greatly enhanced by the immune modulation of the MP that patients may have serious or even life-threatening reactions if they do not start at low enough dosages and do not proceed according to the guidelines.<sup>12</sup> Starting dosages are usually 25 mg minocycline every other day, 1/16 to 1/8 of a 250 mg tablet once every ten days for azithromycin, 1/8 to 1/4 of a 150 mg capsule every other day for clindamycin, and 1/8 of a Double Strength (DS) or Single Strength (SS) Tablet every other day for Bactrim. One must proceed very slowly and cautiously according to the MP guidelines, starting with minocycline, which is added after acclimation to Benicar.<sup>12</sup> The patient must start at these very low antibiotic dosages, even if he or she has previously tolerated much higher dosages prior to the MP.**

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## Marshall Protocol

>

the reversal of many age-related, inflammation-associated conditions in patients on the MP may have implications for the future treatment of many diseases of aging, including cardiovascular disease, diabetes, and osteoarthritis.<sup>33</sup>

J.C. Waterhouse, PhD is the editor of CISRA's *Synergy Health Newsletter*, available at [www.members.aol.com/SynergyHN](http://members.aol.com/SynergyHN), P.O. Box 70166, Pasadena, CA 91117.

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Health Care providers are responsible for the use of this information. Neither the ARF, nor the author, assume responsibility for the use or misuse of this protocol.

Note: Neither the author, Dr. Marshall nor the Autoimmunity Research Foundation have any financial connection with any product or lab mentioned with regard to the Marshall Protocol, and the information needed to do the Marshall Protocol is available free of charge on the Internet study site.



Joyce Waterhouse, PhD, graduated from the University of California, Irvine, cum laude and Phi Beta Kappa, with a bachelor's in Biology. Dr. Waterhouse received a PhD in Systems Ecology with a minor in Statistics from the University of Tennessee, Knoxville. She then pursued postdoctoral research at Oak Ridge National Laboratory. Since 1997, she has written for and edited an online newsletter focused on chronic illness (CISRA's *Synergy Health Newsletter*). She has written a number of articles for peer-reviewed journals, and has recently written a chapter in the book, *Vitamin D: New Research*.

Professor Trevor G Marshall, PhD, has research publications ranging through Cryptorchidism, male and female infertility, insulin infusion, Internet technologies, computer design, and molecular biology. Most recently, he has deduced and published a bacterial pathogenesis for the TH1 immune diseases, including sarcoidosis, rheumatoid arthritis, and chronic Lyme disease. From the pathogenesis, a treatment called the 'Marshall Protocol' has been derived and is being implemented by physicians worldwide. Dr Marshall is a director of the Autoimmunity Research Foundation, patron of the Australian Autoimmunity Foundation, and an Adjunct Professor with the School of Biological Sciences and Biotechnology, Murdoch University, in Western Australia.

### Notes

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# The Use of Lymphocyte Proliferation Assay and Cytokine Production in Seronegative Patients with Lyme Arthritis or Neuroborreliosis

by Aristo Vojdani, PhD, CLS; Bernard T. Raxlen, MD; Shirley Scott, MD

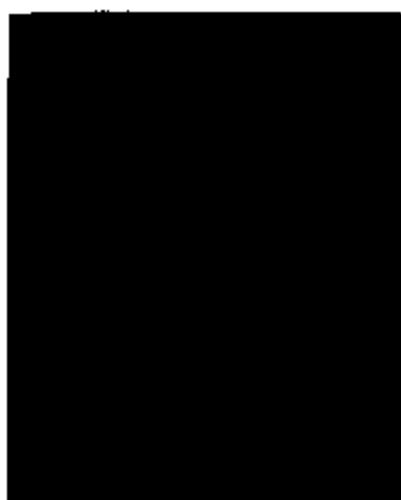
### Abstract

Humoral and cell-mediated immune responses play an important role in the pathogenesis of Infectious diseases, including Lyme borreliosis. Previous studies demonstrated that a specific cellular immune response to *Borrelia*-specific antigens can occur independent of a diagnostic humoral or IgG and IgM immune response. We studied the lymphoproliferative response and cytokine production by mononuclear cells to *Borrelia burgdorferi* antigen of 100 clinical specimens from patients with possible Lyme disease that were sent to our lab for testing. The results are expressed as a stimulation index (SI) generated by dividing the percentage of lymphocytes expressing CD69 or activation marker in the presence of *Borrelia* antigens to the percentage of cells without the antigen. Compared to that of control subjects who had an SI of  $1.6 \pm 0.9$ , 16 out 100 patients showed an SI between 2.1-8.0, with a mean of  $3.9 \pm 2.5$ . Retrospective analysis of data showed that a majority of patients with a high lymphoproliferative response to *Borrelia burgdorferi* antigen were suffering either from neuroborreliosis or Lyme arthritis. In relation to cytokine (IFN- $\gamma$ , IL-10, TNF-

production of IgM followed by IgG antibodies.<sup>1,2</sup> The serum titer of IgM antibodies peaks between 20-40 days after infection. With involvement of T-cells and their response to *Borrelia* antigens, isotype switching from IgM to IgG occurs more slowly. Therefore, IgM titers may wane or remain persistently elevated in patients with Lyme disease. Detection of a new IgM antibody response to different proteins or peptides after two months of infection suggests either persistent active infection or reinfection. Although *Borrelia burgdorferi*-specific IgG antibodies are present in the majority of patients with Lyme disease, a certain percentage of patients with active Lyme disease may not have positive serologies.<sup>3,4</sup> In addition to humoral immune responses, *Borrelia burgdorferi* induces complex cellular reactions to a number of spirochetal proteins in patients with Lyme disease.<sup>4-7</sup> In these patients, specific T-cell proliferative response could be detected when these cells are cultured with *Borrelia burgdorferi* antigens. This lymphocyte proliferative assay is recommended for the diagnosis of Lyme disease, especially in circumstances where serologic tests are equivocal.

### Introduction

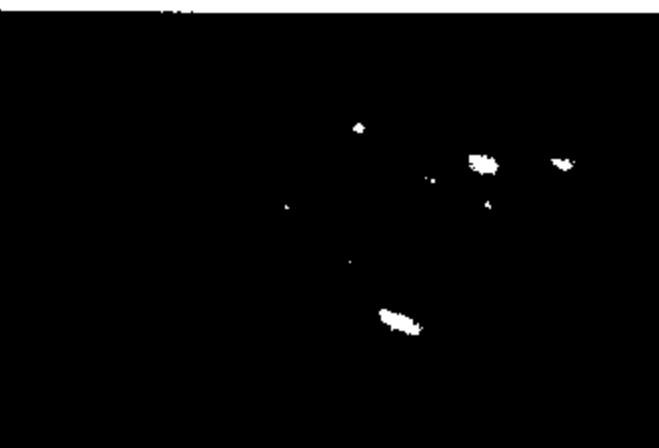
The humoral immune response to *Borrelia burgdorferi* begins within the first few weeks of infection with



Corkscrew form of Borrelia



Cyst form for Borrelia

Borrelia burgdorferi: three profiles in one image  
Cylinder (corkscrew), Cyst (round), and Granular (dots)

In 1988, Dattwyler et al. described 17 patients who were treated with antibiotic therapy for erythema migrans (EM) but subsequently developed attenuated symptoms of late Lyme disease.<sup>4</sup> Although all 17 patients were seronegative, 14 had cellular responses to *Borrelia burgdorferi* by proliferation assay. Subsequent studies not only confirmed these findings in patients with neuroborreliosis and Lyme arthritis, they showed that a significant lymphoproliferative response to *Borrelia burgdorferi* occurs in the majority of patients with cutaneous manifestations of Lyme borreliosis. Further, the study concluded that the lymphocyte proliferation assay may be of diagnostic value in patients in whom Lyme borreliosis is strongly clinically suspected and who have non-diagnostic levels of antibodies against *Borrelia burgdorferi*.<sup>11</sup>

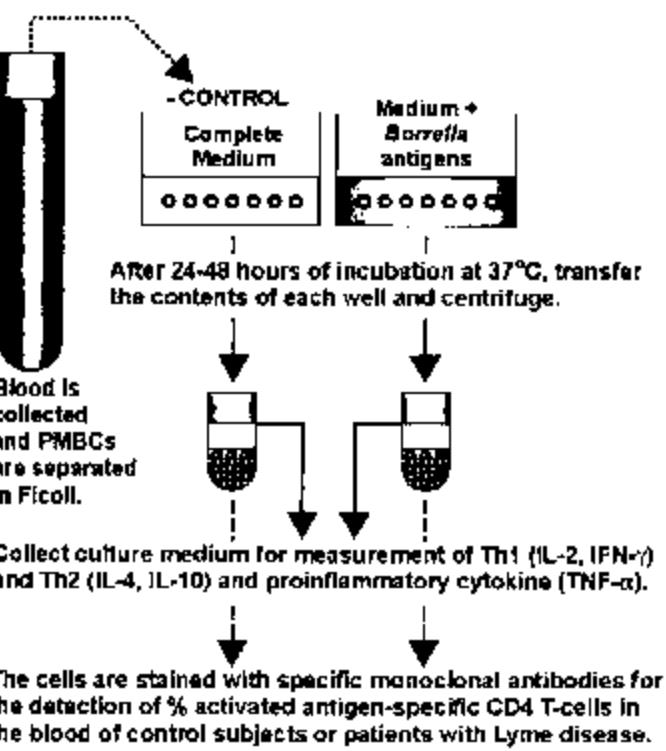
#### Measurement of T-helper 1, T-helper 2, and Pro-Inflammatory Cytokines After Lyme Specific Memory Lymphocyte Culture Assay

Cytokines are involved in regulation of the immune system. Upon stimulation of memory lymphocytes and their reaction to *Borrelia* antigens in culture, not only do these lymphocytes undergo proliferation, they also produce

significant amount of proinflammatory and anti-inflammatory cytokines which can be measured quantitatively.<sup>11,12</sup>

Most of the cells found in the immune system secrete cytokines (normally following activation), and each cell type produces a distinct set of cytokines. For example, upon activation, T-helper-1 (Th1) cells secrete IL 2, IFN- $\gamma$ , and lymphotxin, while T-helper-2 (Th2) cells secrete IL 4 and IL-10.<sup>13</sup>

Both proinflammatory cytokines such as interferon- $\gamma$ , IFN- $\gamma$ , and tumor necrosis- $\alpha$  (TNF- $\alpha$ ) as well as anti-inflammatory cytokines (IL-10) are produced during the course of *Borrelia Burgdorferi* infection. The CD4+ proinflammatory T-helper-1 cells secreting IFN- $\gamma$  have a central role in the induction and perpetuation of Lyme disease and other neurological disorders. Also, macrophages stimulated with the lipoprotein of *Borrelia burgdorferi* produce significant amounts of TNF- $\alpha$ , which plays a synergistic role with IFN- $\gamma$ , resulting in intense inflammatory response. Lipoprotein can elicit not only inflammatory but also anti-inflammatory cytokines such as IL-10 from mononuclear cells present in peripheral blood and synovial fluid.<sup>14</sup>

Figure 1 – Lymphocyte antigenic stimulation and cytokine production by *Borrelia* antigen.

It has been demonstrated that interleukin-10 (IL-10), produced by THP-1 monocytes in response to *Borrelia burgdorferi* lipoproteins, dampens the production of concomitantly elicited inflammatory cytokines. Thus, IL-10 could potentially downregulate inflammatory and microbicidal effector mechanisms of the innate immune response to a *Borrelia burgdorferi* infection, facilitating the establishment of the spirochete. Lymphocyte proliferative response and cytokine production can increase the sensitivity and specificity of Lyme disease diagnosis in an individual with or without seropositivity.<sup>11,15</sup>

#### Materials and Methods

The study population was composed of two groups. Group 1 consisted of 100 subjects with symptoms of Lyme disease whose blood was drawn by different clinicians and sent to our laboratory for measurement of antibodies, lymphocyte proliferation assays, and cytokine production. Group 2 consisted of 40 healthy controls who were in good health with no known disease.

#### Preparation of Peripheral Blood Lymphocytes

Lymphocytes were prepared from fresh heparinized peripheral venous blood drawn in ACD tubes by Ficoll-Hypaque density gradient centrifugation (Litton Bionetics, Rockville, MD). Cells were washed three times with Hanks' balanced salt solution (HBSS), and resuspended to a concentration of  $5 \times 10^6$  cells/mL in a complete medium (CM), that consisted of RPMI/1640 supplemented with ten-percent fetal calf serum and one-percent antibiotics (100 U penicillin and 100 mg/mL streptomycin); within an hour of isolation, the cells were used for the different assays.

Lymphocyte proliferation to *Borrelia*-specific antigens were isolated and tested for mitogenic activity as described earlier.<sup>16</sup> Briefly,  $5 \times 10^5$  lymphocytes per 0.1 mL CM were cultured in flat-bottom microtiter plate wells. Cells from patients and controls were cultured with or without optimal concentration of *Borrelia burgdorferi* antigens purchased from Biodesign International, Saco, ME. After 48 hours of incubation, the cells were harvested, stained with CD69 monoclonal antibody conjugated to

fluorescent dye, and analyzed by flow cytometry. The supernatant was kept for measurement of cytokine production. Wells with cells in medium only were used as negative control. This control provided information about the media and cells used in the assay so we could determine possible nonspecific modulatory activity. The stimulation index (SI) was generated by dividing the percentage of lymphocytes expressing activation marker in the presence of *Borrelia* antigen to that of cells cultured in medium alone. For

this assay, the FastImmune assay of Becton Dickinson, San Jose, CA was used. The FastImmune System, which includes a two-color reagent, CD69 PE/CD3 PerCP, allows customized subset analyses. This allows the functions of specific T-lymphocyte subpopulations to be studied.

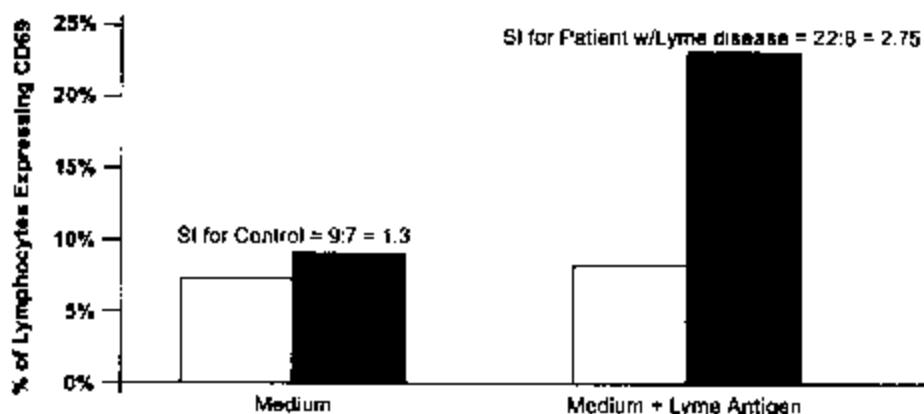
Figure 2 – Lymphocyte mitogenic response to Lyme antigens in controls □ and patients with Lyme disease ■ before and after stimulation with *Borrelia* antigen

Figure 3 – Percentage of lymphocyte proliferative response with SI greater than 2 in health controls □ and in patients with Lyme disease ■.

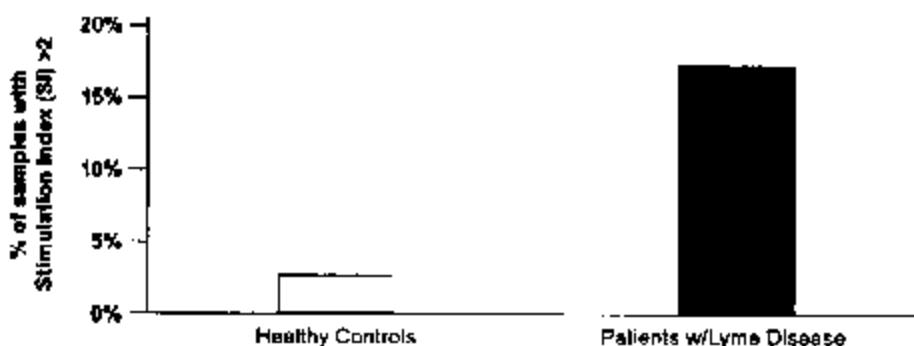
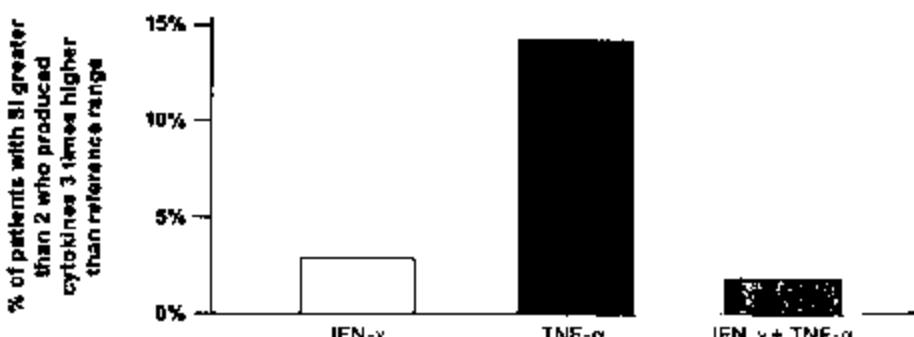


Figure 4 – Pattern of cytokine production by patients of Lyme disease with SI greater than 2.



## Antigen Technology

►

**Cytokines:** IFN- $\gamma$  was measured with a kit provided by R&D Systems, Minneapolis, MN, and IL-10 and TNF- $\alpha$  were measured by the Immulite System from Diagnostic Product Corp. (now Siemens Medical Solutions Diagnostics), Los Angeles, California.

### Results and Discussion

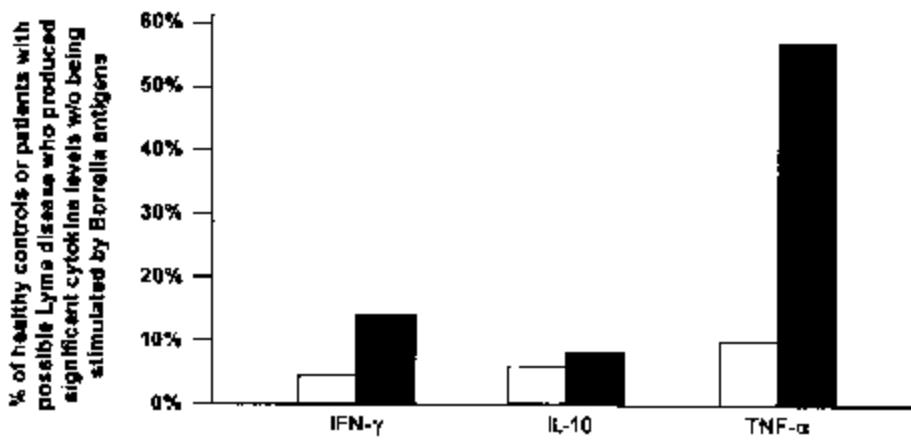
Although *Borrelia burgdorferi*-specific antibodies are present in the majority of patients with Lyme disease, a small percentage of patients with active Lyme disease may not have positive serologies. In these patients, specific T-cell proliferative

response could be detected when these cells are cultured with *Borrelia burgdorferi* antigens. This lymphocyte proliferative assay and cytokine production is recommended for the diagnosis of Lyme disease, especially in circumstance where serologic tests are equivocal.

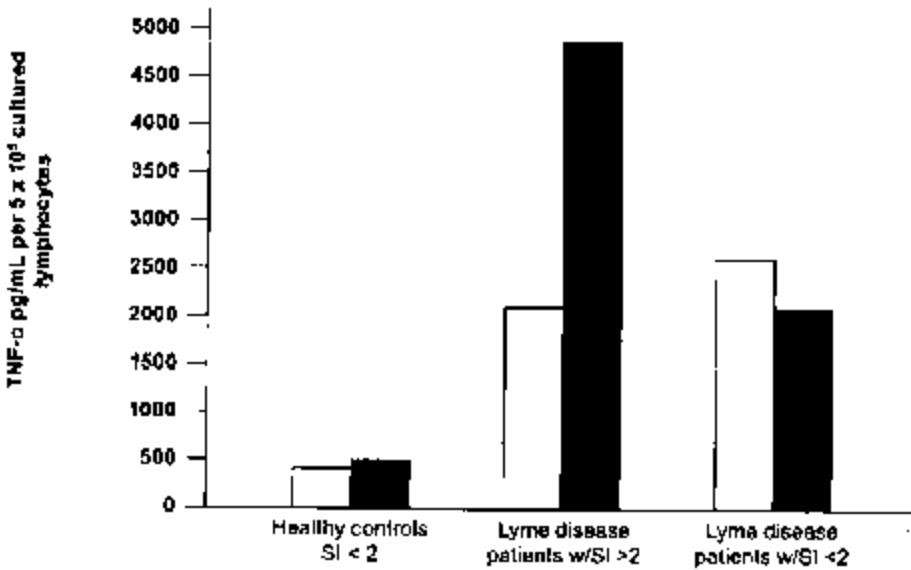
### Principle

In this assay, peripheral blood mononuclear cells including T-cells, B-cells, macrophages, and monocytes are separated by Ficoll Hypaque from neutrophils and erythrocytes and then stimulated in culture media alone or with different concentrations of *Borrelia burgdorferi* antigens (Figure 1).

**Figure 5 – Percentage of healthy controls (white bar) and patients with Lyme disease (black bar) who produced significant levels of cytokines in medium alone.**



**Figure 6 – TNF- $\alpha$  production by healthy controls, patients with possible Lyme disease and patients with Lyme disease with positive lymphoproliferative response to *Borrelia* antigen in medium alone (white bar) or medium + *Borrelia* antigen (black bar).**



Depending on their immune status, a minority of patients with Lyme disease, due to prior T-cell response to *Borrelia* antigens, carry significant numbers of CD4+ T cells in their blood with specific memory for their reaction with *Borrelia* antigens *in vivo*. Upon stimulation with *Borrelia*-specific antigens or peptides, only in patients with Lyme disease will these memory lymphocytes undergo stimulation, synthesize significant amounts of DNA, and express CD69 activation markers on their surface. Staining of these activated lymphocytes by monoclonal antibodies and counting by flow cytometer will allow us to measure the degree of lymphocyte proliferative response to *Borrelia* antigens.

Lymphocyte proliferative response to *Borrelia burgdorferi* antigens with an SI of 1 is considered normal; 1.2 is considered equivocal; and higher than 2 is an indication of prior exposure to *Borrelia* antigens and generation of memory lymphocytes to *Borrelia* antigens (see example in Figure 2). Applying this assay to 40 healthy control subjects with no known disease, the percentage of T-cells expressing CD69 or activation markers from cells cultured in medium alone or in medium with *Borrelia* antigen was almost identical. The mean SI for the controls was  $1.6 \pm 0.9$ , which means that in the healthy controls' blood, an insignificant number of lymphocytes reacting to *Borrelia* antigen carried this memory. In contrast, a subgroup of 16 out of 100 patients with signs and symptoms of Lyme disease showed an SI of 2.1-8 with a mean of  $3.9 \pm 2.5$  (Figure 3).

While we used the CD69 as early activation markers, our results with flow cytometry confirmed the earlier findings; these showed that the SI generated from thymidine incorporation assays used in lymphoproliferative response with *Borrelia* antigens were  $9.8 \pm 9.1$  in patients with erythema migrans (EM), neuroborreliosis and Lyme arthritis in one study,<sup>4</sup> and  $7.2 \pm 1.8$  in a different study.<sup>5</sup> It is interesting to note that the SI in healthy seronegative controls in these studies was  $3.3 \pm 2$ , while in our study it was  $1.6 \pm 0.9$ . These differences in the SIs of healthy controls and patients with our results stem from differences in the methodologies used in the assay, but, overall, patients' SIs are significantly different from those

of healthy controls ( $P < 0.001$ ). *Borrelia* antigenic stimulation of lymphocytes results in the production of cytokines released into the cultured medium.

Supernatants from lymphocytes cultured in the presence of *Borrelia* antigens shown in Figure 1 were removed for measurements of IFN- $\gamma$ , IL-10, and TNF- $\alpha$  (shown in Figure 1). Production and levels of these cytokines by antigen-specific lymphocytes, as shown in Figure 4, were significantly higher in a subgroup of patients with Lyme disease who had an SI greater than 2.0.

In addition, when lymphocytes from 55 patients with possible Lyme disease were cultured in medium alone, they spontaneously produced about a fivefold increase in TNF- $\alpha$  production as compared to healthy controls (Figure 5). When these cells were cultured in medium + *Borrelia* antigens, the level of TNF- $\alpha$  production did not differ from those cultured in media alone. Immunologically, these results mean that 55% of patients with signs and symptoms of Lyme disease have significant inflammation in their systems that may not be induced by the agent of Lyme disease. In relation to IL-10 and IFN- $\gamma$  production, these differences between controls and patients were not significant (Figure 5). This TNF- $\alpha$  production measurement was classified and expressed in three different groups as shown in Figure 6. In healthy controls, TNF- $\alpha$  production in medium (M) was  $422 \pm 290$  pg/mL, while in M + *Borrelia* antigen it was  $518 \pm 361$  (difference = non-significant). In patients with Lyme disease with an SI > 2, TNF- $\alpha$  production in M was  $2.100 \pm 1,600$  pg/mL, which was further enhanced in M + *Borrelia* antigen to  $4,500 \pm 2,300$  ( $P < 0.001$ ). This enhancement in TNF- $\alpha$  production by *Borrelia* antigen indicates that this cytokine is antigen-specific. In patients with possible Lyme disease with SI < 2, although TNF- $\alpha$  production in medium was significantly enhanced to  $2,480 \pm 1,840$  pg/mL, when the same cells were cultured in M + *Borrelia* antigen, TNF- $\alpha$  production did not go higher than the level of that in medium alone (Figure 6). Although the significant elevation in proinflammatory cytokine (TNF- $\alpha$ ) production in medium alone with no further enhancement by M + *Borrelia* antigens confirms the patients' complaints and the inflammation detected by the examining physicians,

this inflammation may or may not be related to the agent of Lyme disease. Where these proinflammatory cytokines are coming from and what agents are responsible for their production is the subject of further research.

### Conclusions

In this study, we demonstrated that the Memory Lymphocyte Immune Function Assay (MELIFA) and cytokine production measurement can support the diagnosis of Lyme disease in up to 20% of Lyme disease patients who may be seronegative, or in patients with equivocal levels of IgG and IgM. Lymphocyte proliferative response and cytokine production not only can confirm a diagnosis of Lyme disease, it can differentiate between patients of Lyme disease and a very high percentage of patients presenting signs and symptoms similar to those of Lyme disease, but which are induced by agents other than *Borrelia burgdorferi*.

The combination of Western Blot assay with the IVIAT Multi-Peptide ELISA, lymphocyte activation, and cytokine production should be used not only for the early detection and management of Lyme disease but also in patients with chronic Lyme disease resulting in neuroborreliosis and Lyme arthritis.

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### Notes

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Dr. Vojdani obtained his PhD in the field of microbiology and clinical immunology with postdoctoral studies in tumor immunology. He is CEO and Technical Director of Immunosciences Lab., Inc. in Beverly Hills, California; member of the editorial board of three scientific journals; and has published more than 100 articles in scientific journals. He is noted for his papers on autoimmunity and neuroimmunological diseases. In 2006, Dr. Vojdani was given the prestigious Herbert J. Rinkel Award by the American Academy of Environmental Medicine (AAEM) for excellence in teaching the techniques of environmental medicine.

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**Title:**

**XRROID ANALYSIS AND HOMEOPATHIC TREATMENT  
FOR CHOLESTEROL AND OTHER BLOOD LIPID DISEASE**

**Authors:**

William C. Nelson, MD.; Homeodiagnostic, Budapest, Hungary  
Wm. J. Cunningham, C. B. T.; Boulder, Colorado, U.S.A.

**Abstract:**

The Xrroid measure of electrophysiological reactivity has been used on many types of diseases. The Xrroid reactivity test was utilized in this study on several patients with excess blood cholesterol versus a control group of patients with correct blood lipid measurements. The testing process was blinded for best results.

In this study the QXCI medical device was shown to be effective in detecting cholesterol excess in the blood. The device was also shown to effective in detecting various heart problems and risks such as infarction.

This article is a summary of the Xrroid reaction similarities in these groups, and we review the results of the homeopathic treatment of the patients with excess cholesterol. This article briefly reviews the electrical reactivity and homeopathic theories and their applications.

This study was performed in 1995-96 in Budapest, London, and Denver Co.U.S.A.

William Nelson 1997.

**XRROID ANALYSIS AND HOMEOPATHIC TREATMENT  
FOR CHOLESTEROL AND OTHER BLOOD LIPID DISEASE**

**Introduction:**

Excess cholesterol can be a result of hypothyroidism, obstructive jaundice, nephrosis, diabetes, pancreatitis, excess alcohol, stress, smoking, oral contraceptives, steroid use, glycogen storage disease, or dietary excess intake of fried and fatty foods. Decreased blood values can occur from hyperthyroidism, infection, malnutrition, heart infarction, malignancies as well as others. Any disorder of lipoproteinemia can be caused or complicated by genetic makeup. The ability to handle blood lipids and lipoproteins differs from individual to individual. Certain people have excellent abilities to handle these excesses where others are quite sensitive. So genetic metabolism is a factor that must be investigated.

The excess lipoproteins will produce pancreatitis, systemic inflammations, glucose intolerance, xanthomas, liver and spleen swelling, sensory neuropathy(leading to tiredness and brain fatigue) weak tendons(from fat deposits), eye disease from excess fat deposits, xanthelasma, and atherosclerosis of coronary and peripheral vessels. This is the number one health problem in the world today. More people will die from this type of disease next year than from all of the other diseases put together. Improper diet from the taste and addictive qualities of saturated fat drive people to over consume foods which complicate and cause the condition. The consumption of proper unsaturated fatty acids (found in raw vegetables) can help to counter this disease. But cooking and other preparations break up the fatty acid chains. Revicci proposed the balance of polar versus non-polar lipids. This is the balance of fatty acids versus sterols in the body. Cholesterol is a key sterol needed in the body for bile and hormone production. It must be balanced with the fatty acids. So part of our therapy of hypercholesterolemia must be a well rounded source of proper cold processed fatty acids.

Other mechanisms of treatment will include niacin(B3 a known vasodilator, which aggravates mental disease in large doses) and homeopathy. Homeopaths for centuries have treated excess cholesterol disease with homeopathic cholesterol. Using the QQC process a more powerful form of cholesterol has been made by New Vistas. Thus our treatment of hypercholesterolemia includes:

1. dietary (decrease red meat, fried and fatty foods, alcohol, processed sugar, while increasing fresh and raw fruits and vegetables)
2. niacin 25 mg a day
3. Fatty Acid Liquesence
4. Cholesterinum QQC

We have been using this treatment for several years with great clinical success.

As part of theory on EPR, the electrical reactivity of a patient to cholesterol will theoretically be an indicator of cholesterol disease. The EPR device Quantum Med C I is a medical device used to measure the reaction patterns of a patient. This device has already been shown as effective in detecting AIDS, breast implant risk, cataracts, and other disease states. Tests of the accuracy of one channel resistance devices that use operator point probes have been largely a failure. These studies have shown these limited one channel devices to be inaccurate. The trivector analysis of the Xrroid system (QXCI) should prove to be a better device for analysis.

So in our need to put clinical investigation to the test we challenge two basic hypothesis. One that the EPR device QXCI can accurately diagnosis lipoprotein disease and two that our natural pharmacology can treat same.

#### **Reactivity:**

Xrroid reactivity has shown that Reductionistic analysis of a patient can be misleading. In fact, a better procedure is that of analyzing the body in its complexity using computer graphic analysis. A review of electrophysiological reactivity should be done at this time [Studies: 2 - 11].

We did see some very interesting individual profiles, which were insightful. Reactivity profiles in cases of AIDS, breast implants, cataract, blood analysis, septicemia, toxic water and other disease states have yielded medical information helpful in developing medical interventions [Studies: 2, 18, 19, 20]. The individual profiles allowed us to understand some of the functioning capacities of the individual patient and led to a more successful homeopathic regime. Taking individual analyses of patients is indeed successful in helping to develop better procedural analysis. The patients were then treated with homeopathic protocols which were individualistic as well, but there were several patterned similarities detected overall in this group.

#### **Method:**

Sixty-two patients were examined with the QXCI device over a 6 month period. Forty-three of these patients had excess levels of cholesterol in their blood analysis. The other nineteen patients (with values within the norms) were used as a control group. The American norms of cholesterol are 120-220mg/dl (conventional), where the European values are 3.1-5.68 mmol/L (S.I. units). These values are taken from the Merck manual. The amount of the cholesterol was compared with correlational statistics to determine the ability of the device to detect excess cholesterolemia. The above norm group was then treated for high cholesterol with the natural intervention listed in the introduction. The blood values were remeasured and the patients reassayed with the QXCI (both retests were taken within two months of the pre test). The reactivity of the QXCI device was compared to mean reactions. Patients with significant reactions to cholesterol versus the mean reaction were considered as reacting.

#### **Analysis Results:**

In the table 1 we can see a brief summary of the results. When we used the Merck Manual list of Norms (high being 220mg/dl or 5.68mmol/L) the correlation was 76% accurate making this a good device for prescreening lipoprotein risks. The existence of excess blood cholesterol was correlated to the severity of the EPR reaction. But when we substituted high values of 195 mg/dl or 5.35 mmol/L a much better correlation was achieved. Using lower values markedly decreased the correlation. Perhaps the Merck statistics are higher than appropriate for optimum health. This could be only seen from a truer value of reactivity such as the EPR technique.

All patients with high blood values dropped those readings in the post test. Lifestyle and awareness alone often result in some simple improvements. Our improvements (reported in percents) seem higher than expected from life style and awareness alone. This would attest to the success of the treatment group. However a statistic control group of lifestyle should be designed into any future study.

Table #1

	PreTest correlation	PostTest correlation	Mean Reduction
High Norm Values	76%	65%	15%
High Values	88%	67%	13%

#### **Discussion:**

The results of the electrophysiological reactivity allowed us to analyze this population for therapeutic similarities. This leads us to conclude that the therapeutic techniques of natural medicine can be successful in treating blood lipoprotein disease. There seems to be a chronic fatty acid deficiency in these patients and an inability for them to manage their fatty acids, hence the need for an oral supplement, Fatty Acid Liquescence. Also, the Cholesterinum helps to reverse the cholesterol syndrome. A review of homeopathy literature [Books: 6 -9, Studies: 1] and the literature regarding electrophysiological reactivity [Studies: 2 - 11] would be important to understand the entire concept and validity of this study.

The accuracy of the QXCI and its trivector approach was seen to be extremely helpful in determining the risk of blood lipoprotein disorders. This supports the EPR hypothesis and further shows its superiority over the one channel resistance point probe systems.

So it appears that complex homeopathy, nutrition and counseling should be considered therapy programs for this pervasive disease, and EPR can be accurate in detecting the disease.

## **XRROID ANALYSIS AND HOMEOPATHIC TREATMENT FOR CHOLESTEROL AND OTHER BLOOD LIPID DISEASE**

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