RES MEDICA
Journal of the Royal Medical Society

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Winter 1967-68, 6(1)
doi: http://dx.doi.org/10.2218/resmedica.v6i1.1967

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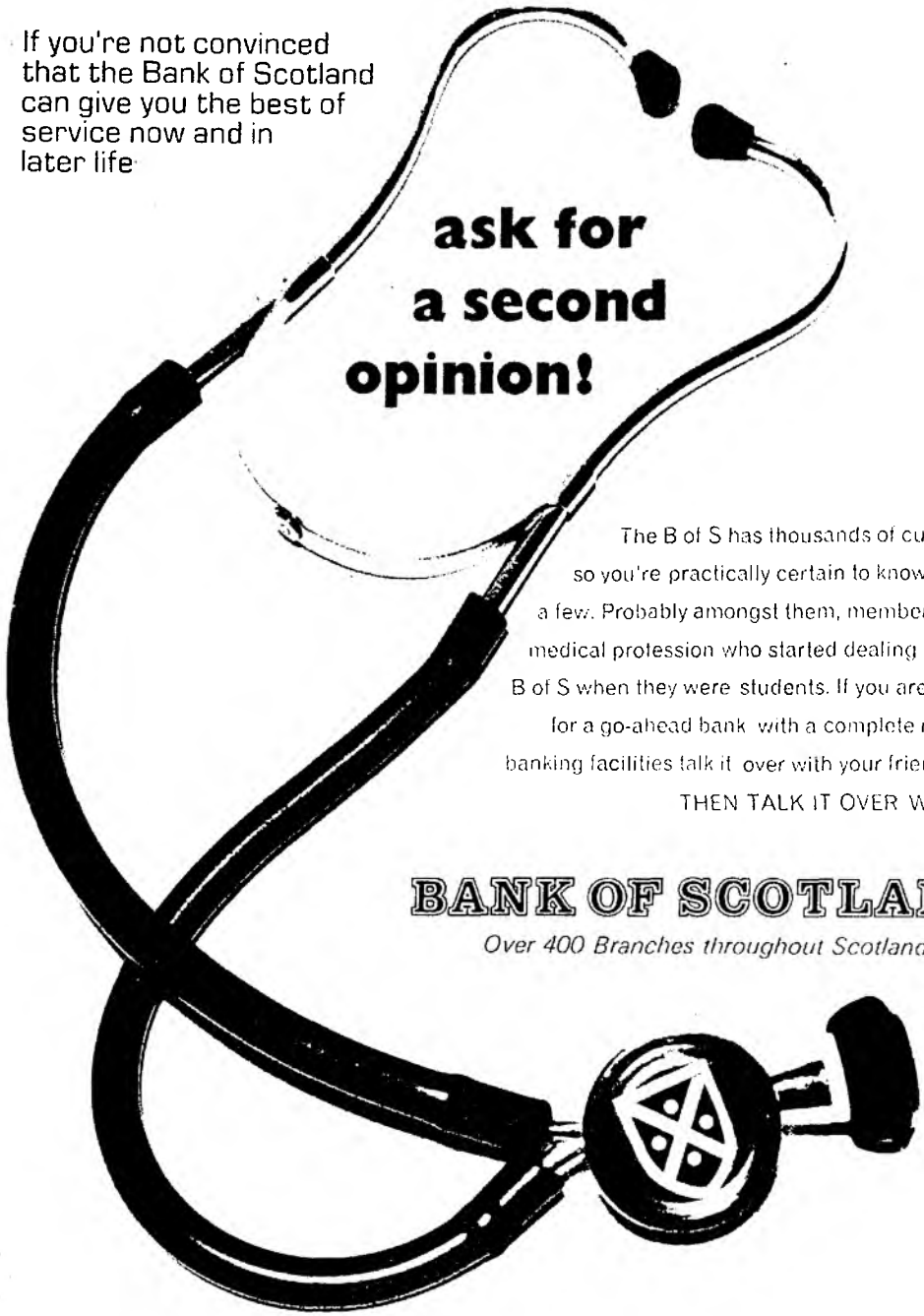

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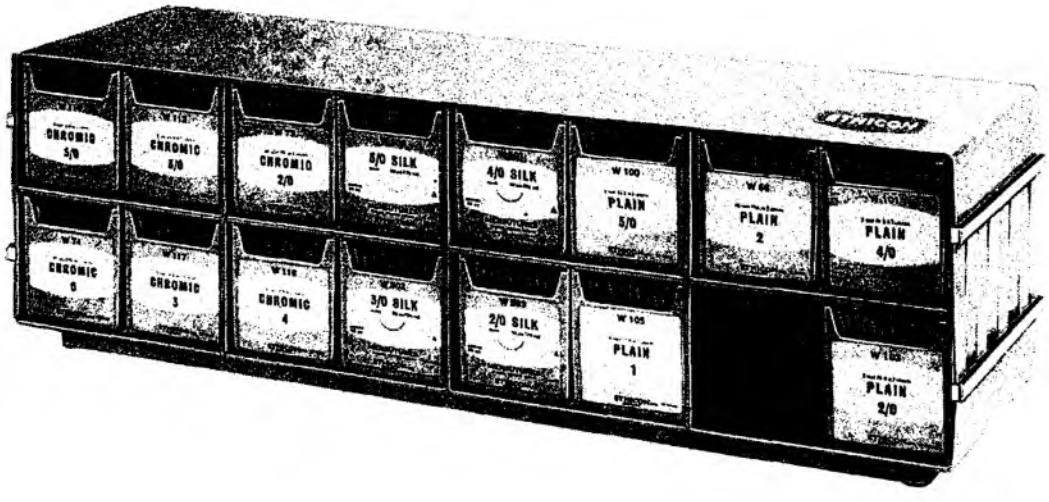

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EDITORIAL

Hippieville is where it's at, or words to that effect. The recent efflorescence of "the scene" has brought its own problems, not the least medical; this could be all too graphically seen in the Haight-Ashbury district of San Francisco this summer where a lemming migration of disenchanted American youth far outstripped the city's hygiene and health provisions. A philosophy of not so much a programme more a way of life does not lend itself easily to adequate sanitation, to efficient screening against infectious diseases, to immunisation programmes for the young and to regular and orthodox nutrition; nor did the defiance of many of the hippies and the irritation of the authorities help matters. Sepsis, upper respiratory ailments, serum hepatitis (from needle injections of drugs) and venereal disease were rife. The collateral dangers from exuberant use of narcotics and dubious pharmacological cocktails further complicated the picture.

An interesting feature of this severe situation was the functioning of the Haight-Ashbury Clinic, run voluntarily by a few doctors, medical students, nurses and social workers. Working on a minute budget, devoted almost entirely to equipment and drugs, they staffed the clinic throughout the summer till lack of funds eventually brought things to a halt in late September. In an area where medical bills normally reach awesome heights this "free medicine" was all the more remarkable. Most of the doctors worked in the clinic at the expense of part of their holidays. While some sympathised with the hippie movement, or were curious about the phenomenon, others presented themselves out of a sense of duty to the crisis, or had personal reasons like the father of a hippie girl who had fled from home for the golden sidewalks of San Francisco. He was not only anxious to find his daughter but was concerned to know more about the attractions that hippie life holds out for the young.

With the end of summer the overcrowding of the Haight-Ashbury was greatly reduced, many of its vacation time inhabitants returning home having had their flirt with 'freedom'. In a subculture such as this, where many of the conventional rules of hygiene and housing were jettisoned, it was rapidly proven that medical and public health amenities cannot be disregarded for long.

THE INVESTIGATION OF A PATIENT BELIEVED TO HAVE A BLOOD DISORDER

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

University Department of Therapeutics, Royal Infirmary of Edinburgh

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

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

THE HISTORY

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

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

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

The Anaemic Patient

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

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

(a) Iron deficiency.

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

Also possible, but less common, are:

(c) Excessive haemolysis.

(d) Marrow failure or replacement.

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

Pointers of importance in the history are:

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

Deficiency of vitamin B_{12} or folic acid

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

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

Whether the patient is a Vegan — an unlikely possibility.

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

A family history of pernicious anaemia.

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

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

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

Folic acid deficiency

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

It is therefore necessary to question the patient about:

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

Pregnancy.

The taking of anticonvulsant drugs.

Symptoms of small intestinal disease, particularly diarrhoea or steatorrhoea.

Excessive haemolysis

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

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

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

Whether or not the faeces are normal in colour.

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

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

Marrow failure or replacement

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

Other Causes of Anaemia

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

BLEEDING DISORDERS

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

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

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

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

A capillary defect, including scurvy.

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

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

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

— the disease has been very mild in previous generations.

— there has been a genetic mutation.

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

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

EXAMINATION OF THE PATIENT

General Appearance

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

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

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

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

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

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

The Face and Neck

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

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

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

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

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

The Mouth

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

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

The Heart and Lungs

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

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

The Abdomen

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

abdomen if the liver or spleen is extremely large.

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

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

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

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

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

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

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

Percussion

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

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

Rectal Examination

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

Nervous System

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

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

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

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

Locomotor System

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

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

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

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

THE RHEUMATOID FACTOR

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HISTORICAL

The observation that certain human sera had the property of agglutinating sheep erythrocytes previously sensitized with specific antibody has been made sporadically since the turn of the century. Only in 1940, however, was this property shown to belong, in the main, to sera from patients suffering from rheumatoid arthritis. In that year, Waaler,[1] working in Scandinavia, published a paper drawing attention to the phenomenon and described a serological test claimed to be useful in the diagnosis of rheumatoid arthritis. Because of the difficulties of communication in war-time, Waaler's work remained largely unknown. In 1948, Rose and his colleagues[2] in New York, unaware of Waaler's observations, "rediscovered" the phenomenon and described a diagnostic test, similar in principle to Waaler's. The observations of Waaler and of Rose and his colleagues have now been amply confirmed and the Rose Waaler test, or more usually one of the numerous modifications thereof, is used routinely as a diagnostic aid in rheumatoid arthritis.

THE ROSE WAALER TEST AND ITS DERIVATIVES

In the original test, complement is removed from the test serum by heating at 56°C. for thirty minutes. Duplicate serial dilutions of the serum are made and to one set of dilutions sheep erythrocytes, previously washed in saline, are added. This titration gives some measure of the concentration of heterophil agglutinins which are almost invariably present in human sera. To the other set of dilutions, sheep erythrocytes which have been sensitized with a sub-agglutinating dose of rabbit anti-sheep erythrocyte serum are added.*

After a period of incubation at 37°C. the titre of the test serum for non-sensitized and sensitized sheep erythrocytes is read. As an example, using serum from a healthy subject the titre for non-sensitized sheep cells might be 1 : 32 and that for sensitized sheep cells 1 : 64. In expressing the result of the test the reciprocal of the titre for sensitized cells is divided by the reciprocal of the titre for non-sensitized cells, in this instance, 64 divided by 32 = 2. The quotient is called the differential agglutination titre or D.A.T. A D.A.T. of 8 or more is generally taken to be a positive test indicating that in rheumatoid arthritis the titre of the serum for sensitized cells usually greatly exceeds the titre for non-sensitized cells. This original test is technically satisfactory, but suffers from the drawback that a "false negative" result may be obtained in a patient with rheumatoid arthritis if a high titre of heterophil agglutinins is present.

Ball[3] in 1950, proposed a modification to the original test to overcome this difficulty. In his test, the serum is first absorbed with non-sensitized cells to remove heterophil agglutinins and then titrated with sensitized cells. The result is expressed as the true titre for sensitized cells. His method is now generally preferred to the original Rose Waaler method and the test has become known as the sensitized sheep cell test, S.S.C.T. or sheep cell agglutination test, S.C.A.T.

* The dose required for sensitization is previously determined by titrating the anti-serum with sheep erythrocytes; thus, if the sheep erythrocytes are agglutinated to a titre of 1 : 1000, which would then be the aggultinating dose, erythrocytes for use in the test would be sensitized by exposing them to one-quarter or one-half of this dose, namely anti-serum diluted to 1 : 4000 or 1 : 2000.

There have been many attempts to increase the specificity and sensitivity of the S.S.C.T., but, in general, it can be said that so far as practical tests for use in a routine laboratory are concerned, any increase in sensitivity is offset by a decrease in specificity.

CLINICAL ASSOCIATIONS OF THE SENSITIZED SHEEP CELL TEST

Rheumatoid Arthritis. The test is positive in about 65 to 70 per cent of patients with adult rheumatoid arthritis. Unfortunately, from the diagnostic point of view, the incidence is considerably lower in patients in whom the duration of the disease is less than one year and in whom certain other stigmata of rheumatoid arthritis, such as the presence of radiographic erosions or of subcutaneous nodules, are absent.

Prospective studies have shown that about one-third of patients remain sero-negative throughout the course of the disease, a further third may fluctuate from positive to negative and a third remain consistently sero-positive.

Polyarthritis, other than Rheumatoid Arthritis. The incidence of positive tests in juvenile rheumatoid arthritis (Still's disease) is low, ranging from about 7 to 15 per cent. Patients with ankylosing spondylitis, Reiter's disease, rheumatic fever, psoriatic arthritis, etc. are generally sero-negative, the incidence of positivity being little greater than in the population as a whole. The incidence of sero-positivity in other members of the group of inflammatory diseases of connective tissue, (including disseminated lupus erythematosus, progressive systemic sclerosis, polyarteritis nodosa and dermatomyositis), is difficult to establish in view of the clinical overlap between these conditions and rheumatoid arthritis. Sero-positivity is most likely to occur in cases of these diseases in which polyarthritis is a prominent manifestation.

Other diseases and healthy subjects. In most reported series, the incidence of sero-positivity in diseases outwith the connective tissue group is around 4 to 5 per cent, this being no higher than in the population as a whole. There are, however, notable exceptions. Positive tests are frequently recorded during the active phase of sub-acute bacterial endocarditis. The test is also postive in about 30 per cent of patients with leprosy and in a smaller proportion of patients suffering from the rather obscure group of diseases characterised by dysgammaglobulinaemia.

About 5 per cent of apparently healthy individuals are sero-positive, but a higher figure is reported in the relatives of patients suffering from sero-positive rheumatoid arthritis. This latter observation has been advanced in support of there being a genetic factor in the pathogenesis of rheumatoid arthritis, but could equally be accounted for by an environmental factor.

THE NATURE OF THE FACTOR RESPONSIBLE FOR AGGLUTINATION OF SENSITIZED SHEEP ERYTHROCYTES

Rheumatoid factor (R.F.) has now been characterised by physicochemical methods. The factor has been shown to be a high molecular weight globulin belonging to the immunoglobulin M (IgM) class. It is most frequently detected in serum, but may also be present in synovial fluid and in other serous effusions in patients with rheumatoid arthritis. Using immuno-chemical methods, R.F. has been demonstrated in plasma cells in synovial membrane and in lymph nodes. It has many of the characteristics of an antibody and forms complexes with globulins of the immuno-globulin G (IgG) class, provided that the IgG has been denatured by physical or chemical means or, in the case of antibody IgG, combined with its specific antigen. On the basis of animal experiments, Glynn, Holborow and Johnson[4] in 1957, suggested that R.F. reacted with sites on the gammaglobulin molecule which only became revealed when the molecule was denatured.

When the globulins in the serum of a patient with sero-positive rheumatoid arthritis are separated by ultra-centrifugation, precipitation will only rarely occur when the IgG and IgM fractions are recombined. If, however, the IgG fraction is heated at 60°C. for ten minutes, and is then added to the IgM fraction (which contains rheumatoid factor), precipitation occurs. On the basis of this experiment, it has been suggested that rheumatoid factor is not only an antibody but an auto-antibody. There is, however, no clear-cut evidence that rheumatoid factor combines with native gammaglobulin *in vivo*.

The ability of rheumatoid factor to precipitate with denatured IgG forms the basis of the

latex fixation test (L.F.T.). Latex particles coated with denatured human IgG are clumped by serum containing R.F. The L.F.T. is simple to do and is more sensitive than the S.S.C.T. but is, however, less specific for rheumatoid arthritis.

POSSIBLE PATHOGENIC SIGNIFICANCE OF THE RHEUMATOID FACTOR

There is now a considerable body of opinion which favours the view that rheumatoid arthritis is an auto-immune disease. This is not the place to discuss the merits and demerits of such a hypothesis but rather to examine the possible role of R.F. in the pathogenesis of the disease.

It seems reasonable to suppose that R.F. is produced by the immune system in response to stimulation by the presence in tissues of mildly altered IgG. There is evidence that IgG is present in the synovial lesion and it has been suggested that its presence indicates an immune reaction, possibly of fundamental importance, occurring in the synovium. If such a reaction should be demonstrated in the future, it is likely that it will be shown to be of the cell-mediated or delayed hypersensitivity type, for it is with this type of immune reaction that the histological appearances in the synovial membrane are most compatible.

The suggestion that R.F. is not responsible for the synovial lesion in rheumatoid disease is borne out by a number of observations. In 1959, Vaughan and Harris[5] transfused high-titre rheumatoid serum to other patients with the disease and failed to promote exacerbation of symptoms. Also, rheumatoid factor has been shown, sometimes in high titre, in unaffected relatives of patients with rheumatoid arthritis and, from time to time, in the sera of apparently healthy subjects. Histologically, it is impossible to distinguish between sero-positive and sero-negative arthritis. An arthritis, very similar to rheumatoid arthritis, occurs in patients suffering from hypogammaglobulinaemia but no R.F. is found in the sera of these patients. Duthie, Brown, Knox and Thompson,[6] in a study of the prognosis of rheumatoid arthritis, showed that patients who were consistently sero-positive fared worse than their sero-negative fellows. It can be suggested from this that in patients with continuing active disease, the stimulus to the production of R.F. by the primary synovial lesion is constantly present.

Although in the main, the evidence is that R.F. is an indicator, rather than mediator, of the primary lesion, there is one manifestation of rheumatoid disease which could be caused by circulating R.F. It has been shown in experimental animals that injection of complexes of R.F. and denatured IgG into the mesenteric vessels may be followed by deposition of complexes in the terminal vessels, thus producing a vasculitis. It seems possible that a similar mechanism might account for the vascular lesions seen in some patients with rheumatoid arthritis, particularly as it is common to find a very high titre of R.F. in such patients.

Finally, although our knowledge of the pathogenic significance of R.F. is incomplete, two observations may give a lead to the aetiology of rheumatoid arthritis. The first, already mentioned, is the high incidence of R.F. in a few diseases of known infective aetiology and the second is the demonstration of Abruzzo and Christian[7] that an "R.F.-like" substance may be detected in the serum of animals hyperimmunised with dead bacteria.

These observations, taken with the obvious compatability of the clinical features and course of rheumatoid arthritis with a chronic infectious illness, have re-awakened interest in the search for an exogenous living antigen in the synovial membrane. Over the past few years a number of centres have reported isolation of a variety of infective agents from rheumatoid tissues. Although none of these agents has been causally implicated in the disease, there is now enough circumstantial evidence to extend this type of investigation. Should it eventually be established that rheumatoid arthritis is caused by a virus, mycoplasma or bacterium (or any combination of the three!) then hopes of a "cure" would be revived and those who find it difficult to believe that individuals turn against themselves — at least without some outside stimulus — would be satisfied.

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Coronary Heart Disease

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A BIOCHEMICAL APPROACH TO DEPRESSIVE ILLNESS

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From a lecture to the Royal Medical Society reporting work carried out by the Unit for Research in Brain Metabolism (Medical Research Council)

We also have a fourth possibility, namely that the changes in metabolism may be taking place only in the brain although the same metabolic process is to be found also in other tissues. If this situation exists it may be impossible to infer changes in cerebral tissue from changes in metabolites in blood and urine.

Studies of cerebral metabolism in depressive illness are necessary in each of the above situations. In 1, 2 and 3 above they are necessary to justify the assumptions relating general and cerebral metabolism, whilst in case 4 the information is not obtainable by any other technique.

TECHNIQUES FOR THE STUDY OF CEREBRAL METABOLISM

Advances in the direct biochemical study of diseases affecting the brain have been made using two main types of technique:

1. The analysis of brain tissue obtained at post mortem or as biopsy material during neurosurgical operation. This technique has been particularly valuable when the biochemical abnormality involves structural components of neural tissue, e.g. in the cerebral lipoidoses.
2. The establishment of animal models of the disease allowing careful control of variables and biochemical studies at varying stages of the disease. This approach has provided valuable evidence, e.g. in the vitamin deficiency states.

The suggestion that depressive illness may be associated with biochemical or metabolic disturbance is not new but added impetus has been given to this approach in recent years by the success of physical methods of treatment, e.g. electroconvulsive therapy and the antidepressant drugs. Studies of electrolyte distribution, adrenal steroid hormones and the metabolism of the biogenic amines have occupied most attention, and excellent reviews of changes reported in depression are available by Durell and Schildkraut, and Coppen (1967).

Biochemical studies in depression. The majority of the published studies have been carried out in relation to "whole body" metabolism, using blood and urinary estimation of metabolites. Whilst we would agree that depressive illness is a disease of the whole person we would argue that the most important and significant disturbances involve the higher nervous functions. Thus studies of general body metabolism will be of relevance only if certain special conditions are fulfilled:

1. If it is known that the whole body changes in metabolism are paralleled by cerebral changes;

or 2. If the metabolites measured in blood and urine have brain as their only source and and are not produced in any other tissue;

or 3. If changes in blood chemistry are found the effects of which are known from previous studies, e.g. hypoxia or hypoglycaemia.

Whilst tests of the biochemical functions of many organs are in regular clinical use, e.g. liver function tests, renal function tests, the design of studies of biochemical functions of the brain in living man are limited by its inaccessibility. Logically it would seem that there are only two practical approaches to the study of the biochemical functioning of the living brain, the estimation of arteriovenous differences of metabolites and the estimation of metabolites released from brain into the cerebrospinal fluid.

In depressive illness the biochemical approach to the brain is further limited for our patients do not die from the disease process, though they may die because of it, e.g. by suicide. In addition we are unable to devise an acceptable animal model of the disease. We must look, therefore, to studies in the living patient to provide us with our information. My colleagues and I in the Unit for Research in Brain Metabolism decided to investigate the possibility of using the release of a cerebral metabolite into the cerebrospinal fluid for the purpose of examining the possibility of a disturbance of amine metabolism in depressive illness.

The Amine Hypothesis — a specific hypothesis relating depressive illness to changes in the cerebral metabolism of the biogenic amines.

A number of biogenic amines are found in brain tissue including histamine, 5-hydroxytryptamine, noradrenaline and dopamine. Whilst there is a rough parallel between the distribution of the amines in brain in that they tend to be concentrated in central structures and basal ganglia, there are also differences in the distribution of the individual amines which suggest specific relationships to certain physiological systems. Studies of the distribution of the amines have been facilitated by the application of the technique of fluorescence microscopy (Fuxe et al (1965)) by which the amine-containing cells and fibre tracts can be visualized in histological preparations. The suggestion that the amines function as transmitter substances at central synapses has received support from the fluorescence microscopy studies. Such studies have suggested a possible role of dopamine as a transmitter in the extrapyramidal system and changes in dopamine levels in parts of this system are reported in Parkinsonism.

5-Hydroxytryptamine is concentrated in parts of the limbic system, e.g. the hypothalamus, amygdala and hippocampus, whilst noradrenaline is concentrated in hypothalamus and mid brain, possibly in relationship to systems involved in central autonomic control.

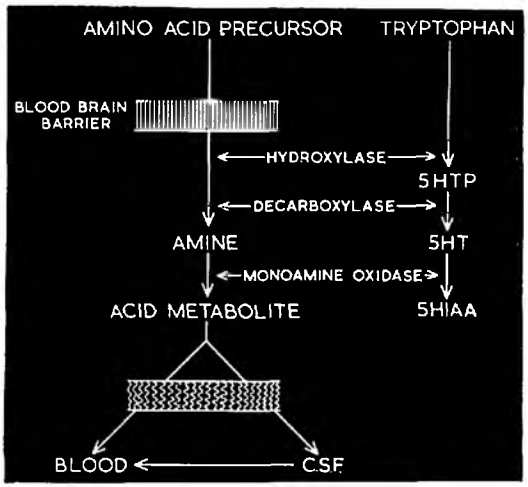
The evidence for a disturbance of amine metabolism is presented by Durell and Schildkraut (1964) and Coppen (1967), and is based on the known actions of drugs which either precipitate or are used to treat depressive illness. In general terms drugs which can precipitate depression in susceptible individuals, e.g. reserpine, reduce the concentrations of 5-H.T. and noradrenaline, whilst the antidepressant drugs either increase brain amine levels (monoamine oxidase inhibitors) or potentiate the effects of the released amines (tricyclic group of drugs). Thus a general hypothesis can be advanced to relate changes in amine metabolism to depressive illness.

WORKING HYPOTHESIS

"That depression will occur whenever the levels of biogenic amines are reduced at reactive sites in Brain".

This hypothesis makes no attempt to distinguish between the relative importance of changes in noradrenaline, dopamine and 5-H.T. metabolism. Our first attempts to investigate this problem were, however, limited to investigation of 5-H.T. Later studies and also studies by Dencker et al (1966) have included studies of dopamine metabolism. To date studies of noradrenaline have been handicapped by the failure to detect its metabolites in cerebrospinal fluid.

The metabolism of 5-hydroxytryptamine in brain is illustrated diagramatically in Fig 1.



The amino acid tryptophan is actively transported from blood into brain tissue where it is hydroxylated to 5-hydroxytryptophan. The 5-hydroxytrytophan is then decarboxylated to the amine 5-hydroxytryptamine which is metabolised to 5-hydroxyindol - 3ylacetic acid (5-HIAA) after release. The 5-HIAA is then cleared into blood directly or via the cerebrospinal fluid. Since 5-HIAA does not pass in the reverse direction from blood to cerebrospinal fluid we argued that the levels of 5-HIAA in the fluid would reflect the levels of the acid in the brain and that this in turn would reflect the turnover of parent amine 5-hydroxytryptamine.

levels of amine metabolites and brain and to investigate the mechanisms for the removal of the acids from CSF.

HUMAN STUDIES

The results of such a study are shown in Table 1. (Ashcroft et al (1966)). They appear to confirm the hypothesis of a disturbance of cerebral 5-H.T. metabolism in depressive illness, the low levels of 5-HIAA in the lumbar cerebrospinal fluid of the depressed patients being consistent with a defect in the release or synthesis of the amine. Further studies revealed a correlation between the severity of the de-

CONCENTRATIONS OF 5-HYDROXYINDOLE COMPOUNDS IN CEREBROSPINAL FLUID

Type of Patient	No.	Site and Method of C.S.F. Sampling	Concentration of 5-hydroxyindoles + (ng. per ml. ± S.D.)	
Neurosurgical	6	Ventricular drainage	88.1 (± 22.6)	
Neurological (organic disease of the central nervous system):				
Neurological Unit	28	Lumbar air-encephalography	33.3 (±11.2)	
Neurological Unit	7	Lumbar puncture	17.4 (± 5.3)	19.1 (± 4.4)
Psychiatric Unit	8	Lumbar puncture	20.0 (± 4.7)	
Alcoholic	6	Lumbar puncture	19.8 (± 2.9)	
Depressed:				
On imipramine	8	Lumbar puncture	8.8 (± 2.4)	10.3 (± 3.8)
On no specific antidepressant	24	Lumbar puncture	11.1 (± 3.9)	
Hypomanic	4	Lumbar puncture	18.7 (± 5.4)	
Schizophrenic:				
Acute	7	Lumbar puncture	10.9 (± 2.3)	
Chronic	7	Lumbar puncture	16.4 (± 2.9)	

* Concentration of 5-hydroxyindoles expressed as 5-H.I.A.A.

(Reprinted from THE LANCET, November 12, 1966, pp. 1049-1052).

The identification of the acid in human cerebrospinal fluid gave preliminary results indicating a difference between the levels in patients with depressive illness and a group of nondepressed patients with neurological disease. Ashcroft and Sharman (1960) suggested that this approach might be a fruitful one. Subsequent studies have been directed to further investigation of these problems and have been of two types:

1. Studies of CSF levels in man;
2. Animal studies designed to examine the relationship between cerebrospinal fluid

pression and 5-HIAA levels and also a return towards normal of the levels with remission from the illness irrespective of the type of treatment (ECT or imipramine).

Confirmation of these results was provided in a study by Dencker et al (1966) who also extended the findings by measuring homovanillic acid, the metabolite of dopamine. Whilst they found the levels of 5-HIAA to be reduced the levels of HVA were within normal limits in depressed patients.

Closer inspection of the results in Table 1 reveals an alternative explanation of the low

levels of 5-HIAA in depression which must be considered before we can accept them as indicating an alteration of cerebral metabolism. In nondepressed subjects there is a gradient in levels from ventricular fluid to lumbar CSF. Fluid obtained at air encephalography which may be considered as a mixture of ventricular fluid displaced by injected air with CSF from other levels has a concentration of 5-HIAA part way between that of lumbar and ventricular fluid. These results suggest that the 5-HIAA is added to the ventricular fluid and removed as the fluid passes down the cerebrospinal axis. Thus low levels in lumbar cerebrospinal fluid could represent either less addition at ventricular levels or a greater degree of removal as the CSF passes down to the lumbar region.

ANIMAL EXPERIMENTS

The relationship between the concentration of 5 HIAA in C.S.F. obtained from different levels of the cerebrospinal axis and the metabolism of the parent amine in brain was thus revealed as a complex one and it seemed unlikely that the problems could be resolved in clinical studies. Animal studies were thus utilised and have provided the vital links in the chain which may now allow us to move forward again with studies in man.

1. *Relationship between Cerebrospinal fluid and brain levels.*

Studies were made using a technique allowing the sampling of CSF from the lateral ventricles and cisterna of the dog and the following results were obtained.

(1) The levels of homovanillic acid in the lateral ventricular fluid reflects the levels of the acid in the underlying brain tissue, i.e., the caudate nucleus. Levels of 5-HIAA are higher than might be expected if caudate nucleus were the only source of the acid and it suggested that structures in the inferior horn of the lateral ventricle, viz. the amygdala and hippocampus, may contribute to the levels. (Guldberg et al (1966)).

(2) The levels of 5-hydroxyindol - 3 ylacetic acid in the cisternal fluid reflect concentrations in mid-brain and hind-brain. (Eccleston et al (1967)).

2. *Active transport of acid metabolites from brain and CSF to blood.*

Experimental studies by Pappenheimer et al (1961) and Davson et al (1962) have demonstrated the presence of a transport mechanism capable of actively transporting certain organic acids, e.g., diodrast and para amino hippuric acid from cerebrospinal fluid into blood. This mechanism appears similar to the renal tubular mechanism which transports organic acid, and the suggestion is made that it is a property of the choroid plexus. We reasoned that the gradient in levels of 5-HIAA noted in our patients between ventricular and lumbar fluid could have resulted from the action of such a transport mechanism and animal experiments were designed to test this hypothesis.

(a) A comparison of ventricular and cisternal CSF levels of 5-HIAA and HVA in the dog revealed a similar gradient to that observed in man.

Pretreatment of the animals with probenicid, a drug which blocks the renal transport mechanism for organic acids, was shown to reduce significantly the gradient levels of 5-HIAA and HVA between ventricles and cisterna with a marked relative rise in cisternal acid levels. Guldberg et al (1967). Such a result is consistent with the presence of an active transport mechanism for the organic acids situated in the CSF pathway.

(b) A technique was developed for the perfusion of the cerebral ventricles in the conscious dog similar to that used in the goat by Pappenheimer (1961). Such a method (Ashcroft et al (1967)) was used to study the clearance of 5-HIAA and HVA and inulin from the CSF, the results confirming the presence of an active transport mechanism for the acids and localising it in the fourth ventricle. Neff et al (1964) have provided evidence for a similar transport mechanism for 5-HIAA from brain tissue to blood.

CONCLUSIONS

The studies described in brief above represent an attempt to develop a technique for the study of the cerebral metabolism of 5-hydroxytryptamine in patients with depressive illness. The progressive evaluation of the technique has required the use of animal experimental procedures to examine the relationship between CSF and brain in addition to studies in man.

Our simple model (Fig. 1) must be amended in light of these studies to show a variation in 5-HIAA levels with the site of CSF sampling

and to include the concept of active transport rather than the passive diffusion of acid metabolites from brain and CSF into blood.

The results of the CSF studies in depressed patients showed lowered levels of 5-HIAA but normal HVA levels in lumbar fluid. Such a selective lowering of 5-HIAA levels argues against an increased rate of transport of the acid from CSF as disturbance of such a mechanism would be expected to lower concentrations of both HVA and 5-HIAA. We must conclude, therefore, that the findings appear to indicate a diminished release or synthesis of the amine 5-hydroxytryptamine in the brain of the depressed patient and would suggest that the most likely defect is in the hydroxylation of tryptophan.

The results, however, give us only a glimpse of the problem and the investigations have left us with more questions to answer than when we started, e.g. are the symptoms of depressive illness causally related to the change in amine metabolism? Do different depressive clinical syndromes have different associated biochemical findings? Can the biochemical findings be shown to have any predictive value in terms of treatment and prognosis?

Acknowledgments.

In this paper I have concentrated on the technical aspects of an investigation which also has important ethical considerations. Our patients' permission for the investigations was sought after a full explanation of the nature of the tests and we would like here to acknowledge their ready co-operation. I wish to emphasise that this investigation was carried out by a team of workers.

In addition to those referred to in the text I wish to extend thanks to the medical and nursing staffs of the Royal Edinburgh Hospital and particularly to Dr. Elizabeth Robertson and Professor W. L. M. Perry.

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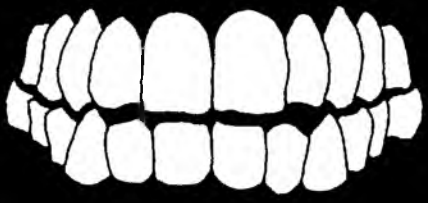
Duel Purpose

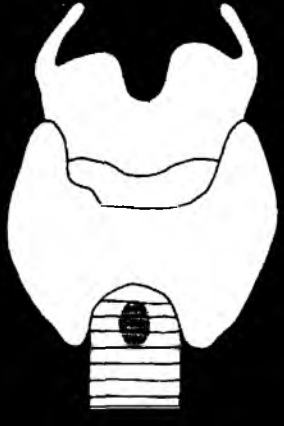
"Hence, notwithstanding a most keen and illiberal persecution, which the new doctrine sustained from Cullen and his adherents, the disciples of Brown, from their numbers, shortly became so formidable to their adversaries that the latter, upon all occasions, and in all public societies, were perpetually annoyed and molested by them. The palaestra, where their contests were maintained with the greatest violence, was the Royal Medical Society. Here the partisans of both doctrines used to assemble weekly; and the debates on each side were conducted with such vehemence and intemperance, that they very commonly terminated in one member calling out another to the field. Such encounters had so frequently disgraced the Society, that, in order to prevent the growing evil, it became necessary to pass a law, by which it was enacted, that any member, who challenged another, in consequence of what had been said in the public debates, should be expelled the Society."

—from a Biographical Account of Dr. John Brown by William Cullen Brown (1804): John Brown was President of the R.M.S. three times, and during his third term of office published the "Elementa Medicinæ", expounding his system of medicine which raised a great deal of controversy in Edinburgh, but had more success on the Continent.

drink it



chew it



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"JAMES MACKENZIE : RESEARCH IN GENERAL PRACTICE"

by DAVID McLEOD, B.Sc.

From a dissertation read before the Society on Friday, 20th October, 1967.

Born the son of a Highland farmer in 1853, near Scone in Perthshire, James MacKenzie was destined to become a leader among medical men. He utilised the opportunities of a general practitioner to study the early symptoms of disease and the bearing of the disease on the patient's future life.

In defining how this came about, three main factors seem to emerge as especially significant in his early years. As an apprentice to a Perth chemist, he found that his "natural bent lay in a practical rather than an academic direction". In his preclinical years at Edinburgh University, he experienced some difficulty in passing examations, for they were contrived for the purpose of testing memory rather than the power of reasoning — MacKenzie had difficulty in remembering isolated facts, but if facts were "related in some consecutive manner, they could not only be remembered, but their bearing on one-another fully appreciated". Thirdly, MacKenzie studied in Edinburgh at a time when the medical school was undoubtedly the foremost in Great Britain — the "very vanguard of new ideas in medicine and surgery". Here MacKenzie's scientific outlook was nurtured and his inquiring instincts sharpened by his training in the midst of the controversies of the Listerian era, and further stimulated during his membership of the Royal Medical Society in 1878.

BANK PARADE, BURNLEY

In 1879, he entered the largest general practice in England at that time at 68, Bank Parade, Burnley. It has been commented that "there was nothing in his environment to stimulate him to do anything more than conscientious routine work in the diagnosis and treatment of cases" — but on the contrary, MacKenzie found inspiration in both his professional colleagues and the lot of his patients.

The senior partner in the firm was Dr. William Briggs, and it was his confident certainty about the outcome of his patients' illnesses that started MacKenzie off on his long study of prognosis. That such a study was vitally necessary became apparent to MacKenzie as he worked among the people of the Lancashire cotton town.

Burnley lay in the wake of the Industrial Revolution during which time it had become a "shocking mix-up of mills, foundries and pits", each surrounded by rows and rows of back-to-back houses. The lower-class population was outrageously exploited by the factory employers, wage disputes causing grim strikes and frequent unemployment; the widespread drunkenness and crime, plus an absence of adequate sanitation, further added to the misery of the inhabitants. Contagions abounded — epidemics of cholera, typhoid, smallpox, diphtheria and scarlet fever were commonplace, children under five years being particularly accursed.

As MacKenzie worked among the poorest families in the town, he soon came to recognise the need for accurate prognosis, for he would sense the fear that lay behind such questions as "What is going to happen to me?", or "When can I get back to work?" When the only means of employment involved strenuous labouring in mine, mill or foundry, his answers

to such questions became of critical import; for advising a patient to rest might condemn him to complete idleness and his family to poverty, the workhouse or starvation.

But upon what principles could he base an opinion? He did not have Dr. Briggs' "clinical instinct", and had neither learnt in Edinburgh, nor could find in the literature any indications as to the prognostic significance of the signs and symptoms which his patients presented; he was similarly disturbed to find that he knew nothing of the mechanism of these signs and symptoms.

MACKENZIE'S POLYGRAPH

Mackenzie is perhaps best known to undergraduates as the co-inventor, with a Padiham watchmaker, of the Ink Polygraph (the poor relation of the Electrocardiograph), with which he could simultaneously record arterial and venous pulsations. Yet I feel that a prolonged description of this and earlier instruments and discussion of interminable polygraph traces would not really be a fitting tribute to MacKenzie's work.

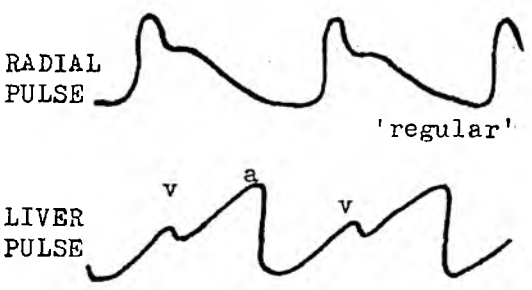
In his practice, MacKenzie saw a great deal of cardiac failure which was largely of rheumatic origin, and a single case history will serve to illustrate his experimental findings and his progression of thought concerning his patients and their traces. In 1892, he attended a woman of 42 years who had a history of four attacks of rheumatic fever; a presystolic murmur had followed and had become more pronounced, indicating progressive mitral stenosis. At this time, the woman suffered from weakness and some shortness of breath: on examination, her apex beat was in the 5th space, the neck veins were not raised and the liver was two finger-breadths below the costal margin and pulsating. Her Kymograph traces were largely normal:

(Figure 1)

This pattern continued for some years until in 1898, and with dramatic suddenness, she was seized with great breathlessness and distress, and was found to be in marked failure and extremely ill. On examination, her pulse was very rapid and irregular both in time and force; MacKenzie knew this pulse as the "Dangerous Type of Irregularity". The apex beat was in the 7th space, and the liver was three inches prominent and pulsating; there was a large J.V.P., and the ventricular form of the jugular venous pulse (showing absence of "a-waves") was recorded:

(Figure 2)

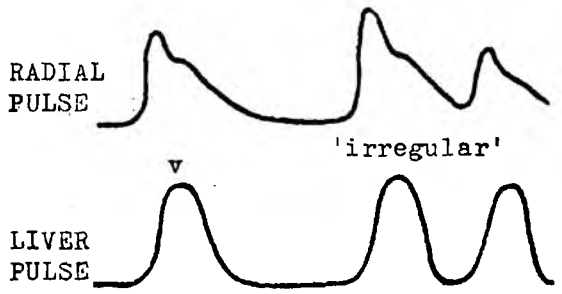
Fig. 1.



'a' = wave due to atrial systole.

'v' = wave corresponding in time to (late) ventricular systole.

Fig. 2.



N.B. no 'a'-waves.

However, on auscultation, MacKenzie was perplexed to find that the presystolic murmur, which had persisted in this heart for over 18 years, was absent! He discounted the possibility that the narrowed valve had opened up again, and dismissed the current view of the day that in failure, when the right ventricle dilated, it pushed the left ventricle away from the chest wall so that the murmur could no longer be heard.

Then the truth came to him; the absence of the 'a-wave' in the J.V.P. indicated that the auricles had ceased to contract, this contraction against the resistance of the stenosed valve having formerly produced the presystolic murmur. When the woman died a year later, MacKenzie found greatly distended, thin-walled atria at post-mortem. He considered that the

atrial distension precluded its rhythmical contractility and thus coined the term "auricular paralysis"; however, he could not explain the ventricular irregularity on the basis of such a paralysis: full elucidation came from Sir Thomas Lewis' studies of junctional tissues in the heart, and from E.C.G. findings was evolved the term "atrial fibrillation".

By such investigations, then, MacKenzie showed that the inability of the heart to maintain the circulation may be due to a disorder of any of the factors upon which normal heart action depends e.g. its rhythm, the condition of the valves, or inherent defects in the myocardium.

Now, MacKenzie's investigation of heart failure was an extension of his work in the busy Burnley practice; all who enjoyed his hospitality at Bank Parade, including Osler, Cushny and Wenkebach, marvelled how this hard-worked G.P. could fuse so successfully with the enthusiastic research-worker. His discoveries resulted from the collection of scientific experimental data and the employment of sound reasoning; he always insisted that it is the analysis and consideration of recordings that is important in research, and he would sit for hours thinking over his patients and their traces, often in the early morning after a cold bath, or in the evening while his wife played the piano to him.

WAIT AND SEE

In addition to recognising the meaning of signs and symptoms, MacKenzie appreciated the importance of knowing what bearing they may have on the patient's prognosis. He had been much impressed by Dr. Briggs' ability to foretell the outcome of his patients' illnesses, but was dismayed that this knowledge could not be passed on to new generations of doctors. It then occurred to him that Dr. Briggs' mysterious power was nothing more than accumulated experience — every time his senior partner considered a new case, he remembered hundreds of old cases and how they had fared. Thus MacKenzie began his "wait and see" method of defining prognosis i.e. in order to assess the prognostic significance of any symptoms, patients presenting the symptom would be watched over a period of years to determine what happened to them.

By this means, he began separating the dangerous from the benign forms of pulse irregularity; knowledge of the pulse had been "not merely imperfect, but chaotic", he said, for though these irregularities were easy to recognise, their "significance was completely misunderstood".

MacKenzie came across many children demonstrating the "Youthful Type of Irregularity" (sinus arrhythmia), where the heart rate varies with the phase of the respiratory cycle. His "wait and see" method proved to him that the condition was physiological — he found the irregularity distinct in perfectly healthy children, and in watching them grow into adulthood, noted that they never showed any signs of cardiac weakness. However, he was dismayed to find that outside his practice, such children were variously treated, and when these failed to remove the supposed affliction, the children were labelled as "incurables" and told to restrict all physical activities.

The benign nature of sinus arrhythmia is now a standard part of medical knowledge, yet the discovery of this is seldom attributed to MacKenzie's method; this 'negative aspect' of his work has been considered less valuable than his polygraph traces, but surely, as MacKenzie himself once remarked, his "greatest contribution was to have freed a large number of people from fear". Hence the saying — "Cupid never broke hearts so fast as MacKenzie mended them".

Similarly with regard to the "Adult Type of Irregularity", (the premature systole), he was again confronted with the "universal idea in the medical mind that something mysterious is very much amiss with the heart that presents an irregular rhythm". He demonstrated that the premature systole indicates ventricular stimulation prior to the termination of normal disastole, such stimulation being either momentary (giving rise to a single missed-beat) or lasting for longer period (producing a "stumbling" pulse). And after years of observation of hundreds of patients, his method of "wait and see" proved to him that "the irregularity is perfectly consistent with good health . . . and a sound heart". That is not to say that no significance should be attached to this sign: it is commonly present in patients who are dangerously ill e.g. with valvular heart disease or chronic nephritis, and who died from congestive failure, but "then it is only one of the many symptoms that testify to the weakness of the heart", he said, "and is of no serious significance in itself".

As a result of this work, he propounded his "law of associated phenomena" i.e. " a serious prognosis should not be given on the evidence of a single symptom or sign". Thus, the pre-

mature systole has no consequence when it is the only abnormal sign or occurs in mild cardiac failure.

BELOVED PHYSICIAN

Although MacKenzie's findings were very slow to be accepted (and on occasion were actively resisted) in the great centres of medical learning, the doctor was loved and revered by his patients in the Burnley practice. There was no "hush of self-importance" about him as he travelled about the town in the first motor car to be seen there, and he always explained his methods to his patients and the reasons behind his diagnosis. Above all he considered it a duty to tell every patient (or those responsible for him) the likely outcome of his illness. His colleagues marvelled at the confidence in him which the dying and distressed displayed; small wonder he came to be known as the "beloved physician".

PRINCIPLES OF PROGNOSIS

Although MacKenzie had defined the mechanism of various pulse irregularities — sinus arrhythmia, premature systoles and auricular paralysis — his wait and see method had only demonstrated that the former two were benign; of auricular paralysis, he knew that some patients die soon after the commencement of the irregularity while others go on for years with little trouble; he was thus still unable to recognise the earliest signs of heart failure, and thereby foresee danger in the patient's future.

About this time, he was pondering over the contrasting prognoses of a patient with premature systoles as the only abnormal sign, and another showing no abnormality on clinical examination yet who would be seized with a spasm of anginal pain on walking 100 yards. He conceived that the earliest symptoms of heart failure are shown in a response to effort, and thus evolved his great principle that "the first sign of heart failure is a diminution in the reserve force of the heart muscle". The extent of the response to effort offers the most valuable aid in judging the efficiency of the heart and circulation and hence in assessing the patient's prognosis.

He thus taught that attention must be paid to symptoms as a guide to prognosis, the "commonest being shortage of breath, occurring on such exertion as the patient was wont to undertake without discomfort".

Artificial tests like asking a patient to hop about a room and then counting his pulse or taking his blood pressure, are of little value; the information required to make an estimate of the amount of reserve force is obtained from the patient's own experience of responses to exertion e.g. walking up a hill after a meal or into a wind.

A story is told of a visit by MacKenzie to the Royal Infirmary of Edinburgh, during which he was asked to opine on the circulatory condition of a woman awaiting cholecystectomy. She had been found to have anomalous heart-sounds, and the surgeon doubted the wisdom of operating (for as with irregularities, murmurs, of whatever nature, were considered to be of serious significance at that time). MacKenzie talked to the woman before a crowd of onlooking staff and students, and soon learnt that she lived in a top flat and shopped for a family of six, finding no difficulty with the stairs. He straightaway told the surgeon to operate with confidence so far as the function of the heart was concerned. The crowd drifted away, disappointed at seeing nothing of the famous man's skill in examining a patient, and largely unappreciative of the important lesson which he had taught them.

CONCLUSION

So MacKenzie, hailed as the inventor of the polygraph and a leader among research scientists of his day, always maintained that bedside evidence, particularly the patient's history, was always of primary importance over instrumental and laboratory evidence at second hand. He taught that pulse irregularities and murmurs achieve significance entirely by virtue of their relationship to, or effect on, the heart's efficiency as a pump (as reflected by a patient's symptoms during responses to effort).

As a family doctor, MacKenzie knew his patients in health as well as disease; it was only while working among the people of Burnley that he learned the need for the information which his researches were to give him, and it was only in general practice that he could carry out these studies, for there he saw his patients throughout the whole course of their illnesses.

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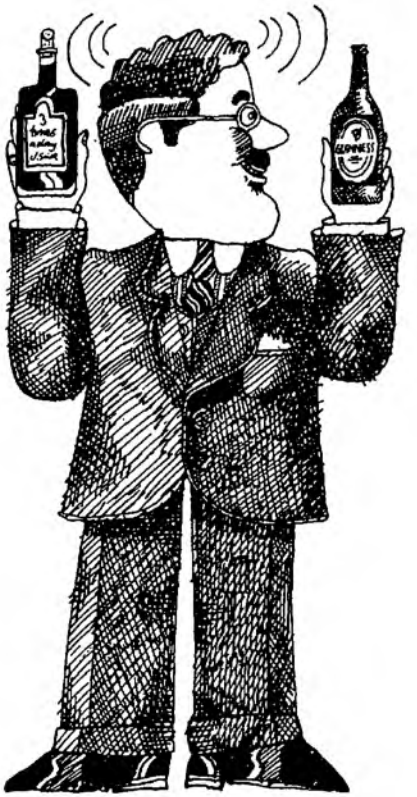


G hastly potions often must,
U nhappily, be swallowed;
I t's from such nastiness (we trust)
N ice cures have often followed.
N one the less, it's great to find
E xpressly recommended
S tout which does to all mankind
S uch good while tasting splendid.

G.E.4396R

DIAGNOSTIC PROBLEM

Set by SANDY DAVISON, M.B., Ch.B., B.Sc.

(answer on page 37)

Subject: A.L., 40, male.

Presentation:

1. abdominal distension for a week prior to admission
2. vague peri-umbilical pain: constant, radiating to back and groins, not relieved by antacids or warmth
3. nausea and vomiting of coffee-grounds material, followed by bright red blood, on evening prior to admission

Enquiry:

P.H. "hepatitis" two years previously
F.H. father d. C.V.A.; mother d. pneumonia; brother d. alcoholism
S.H. 20 cigarettes/day; previous treatment for alcoholism
Systematic: occasionally jaundiced; otherwise N.A.D.

Examination:

Jaundiced; spidery naevi on face and shoulders; no lymphadenopathy; smelling of alcohol
C.V.S. pulse 80, B.P. 120/80; heart N.A.D.
A.S. abdomen distended; peri-umbilical and bilateral loin bruising; fluid thrill; shifting dulness present; liver palpable 3 fingers below costal margin; tip of spleen palpable; no tenderness; F.O.B. positive.
R.S. dull at both bases.

1. What is the differential diagnosis?
2. What investigations would help in determining the diagnosis?

● The Presidents' Annual Dinner, with guest of honour Sir Max Rosenheim, attained its traditional level of elegant conviviality. Wine and wit flowed merrily enough and once more it became hard to imagine how the Society could ever have conducted such an evening without the grace (and organising ability!) of the ladies. The formality of the dinner has always occasioned the wearing of white ties and tails by the chief guests and hosts. However this year continued the trend towards the wearing of the simpler black tie and dinner jacket and although a certain uniformity of dress is aesthetically preferable it would be a pity if any difference of opinion about what constitutes suitable attire were to blossom into a big-enders versus little-enders struggle.

● At the suggestion of Sir John McMichael F.R.S., a former Secretary of the Society, and with the invaluable help of Drs. Julian and Oliver of the Department of Cardiology, and Dr. Falconer of the B.M.A., the Society arranged a Symposium on "Angina Pectoris" to commemorate the first use of amyl nitrite in this condition by T. Lauder Brunton while he was Senior President of the Society.

Papers ranged from coronary arteriography (Dr. Richard Gorlin, Harvard, and Dr. G. C. Friesinger, Johns Hopkins, Baltimore) and experimental studies on the coronary circulation in dogs (Dr. Russell Rees, Westminster Hospital), to epidemiological studies (Professor Morris, London) and the benefits of anticoagulant therapy in the prognosis of angina pectoris (Dr. C. Borchgrevink, Oslo). Two present members, Mr. Robin Hunter and Miss Alison Leach, gave short papers on "Lauder Brunton" and "History of Angina" respectively. The meeting was concluded by a panel discussion chaired by Dr. Julian.

A celebration dinner was held in the Royal College of Physicians, at which Sir John McMichael was the principal speaker, while the Symposium itself was held in the hall of the Royal College of Surgeons; to both Colleges the Society extends its gratitude.

● After many months of preparation and deliberation the alienation of a major portion of the library by sale was finally ratified at a private business meeting in November. Ironically, the convocation of a constitutionally acceptable gathering proved as tedious as the ultimate decision was swift. A sense of anticlimax did not however diminish the historical significance of the procedure. Negotiations now continue with those firms interested in its purchase. Sed tempora mutata sunt et nos mutamur . . .

● The starting of a "Journal Club" is applauded. Discussions at Thursday lunch breaks will deal with current medical topics and is yet another sign of the increasing use the Society's premises are being put to — the clean and warm surroundings proving a strong attraction to members during the week.

● In a valedictory address sensitive to the situation of the patient in a National Health hospital, last year's Senior President, Matthew Kaufman, had this to say: "The position of the patient in hospital is a particularly unenviable one, being in all but a few instances bottom of the hospital hierarchy. Here the chain of command moves from top to bottom while information of the patient's needs percolates only slowly through in the opposite direction. In this feudal state the patient is the serf, vulnerable to the whims of his masters, deprived of clothing to the limits of decency, and subjected to a form of regimentation even worse and possibly more pointless than that once experienced by many in National Service. Visiting hours are usually inflexible, even though a Government memorandum in 1962 stated that "visiting should be regarded as an important contribution to the patient's recovery, never as a concession or as an unwelcome interference with hospital routine" . . .

"A climate of good exchange of ideas and feelings is not induced by the doctor who goes round the ward talking to those around him

about the patient, without including the patient in the conversation. It may be argued here that the consultant going round the ward has no time to give this kind of care to each patient, and that he expects this to be done by junior members of staff; in most wards this is done by junior members but communication is most satisfactory to the patient in those wards where senior members of staff 'treat the patient as a whole'. In such wards junior members of staff appear to follow the example of their consultants and pay particular attention to the communication needs of the patient.

Unfortunately, although the hospital population today has changed in that hospitals are no longer catering solely for the sick poor, there is still a marked professional distance between the doctor and his patient, even where patients of other professions are involved.

In general, patients accept medical students feeling that in some small way they are giving something in return for the care received. Some positively enjoy teaching sessions as they help to pass the time, they present a possible opportunity for finding out what's wrong with them, and, in some instances, being taught on is regarded as a status symbol.

Often patients are inadequately prepared or warned that they are to be the subject of a lecture or demonstration. As a result of this, considerable confusion ensues in the mind of the patient; far from learning more about his particular illness, he is often erroneously led to believe that he has several other illnesses as well.

Overlong interviews prove tiring, and the repetition of information irksome, while failure on the student's part to introduce himself may cause unnecessary anxiety. This is more especially the case when the patient is interviewed in the ward by a man in an ordinary suit with no white coat and no stethoscope, who shows particular interest in personal problems, or, for example, in the circumstances of injury or accident.

This is due to thoughtlessness, nothing else, and certainly is not confined to the medical student. However competent the surgeon or physician, some of the effectiveness of his skill is lost to the patient if the manner in which it is used shows lack of consideration for the patient as a person with thoughts and feelings."

● Raising the price of this Journal has been a regrettable but necessary step. In these days of pricey pie 'n pints it is hoped that your outlay of two shillings will have been amply justified. The Journal continues to be grateful to its honorary editorial board for their co-operation in business matters, and to Mrs. Thompson and Miss Harkins for their willing help. An error in our last issue should be corrected: in "The Chocolate Coated Pill" the sequential therapy type of pill mentioned involves the administration of oestrogen from days 5 - 20, and not progestin. We apologise for any confusion caused.

● The Society has had a hand in the founding of the Edinburgh Medical Group. While it is to early to assess the value of such a venture, designed to air the topical, the complex and the obscure in medicine and allied fields, there is at least a healthy stirring to comprehend more about the difficulties inherent in medical advance. Will it herald the teaching of philosophy in the medical curriculum once more?

SYLLABUS FOR THE SPRING TERM

January

12 Address: Prof. George J. Romanes. "Peripheral Nerves" (in Surgeon's Hall)
19 Dissertation: Dr. Sheila Picken, "Medicine at the Time of Shakespeare"
26 Talk: Dr. D. C. Simpson, "Powered Prosthetics"

February

2 Dissertation: John B. Irvine, "Stereognosis"
9 Dissertation: E. John Elliot, "De Dementia Praecoci"
16 Address: Prof. Michael F. A. Woodruff, "Experiences with Renal Transplantation" (in Surgeon's Hall)
23 Dissertation: John D. Corson, "Arthritis as a Manifestation of Systemic Disease"

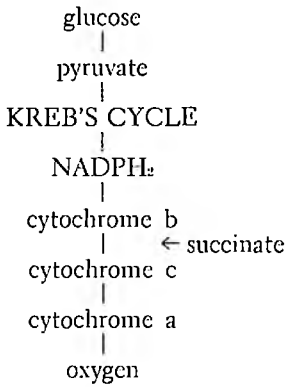
March

1 To be arranged.
6 Annual Extraordinary General Meeting
8 President's Valedictory Address

ON THE MODE OF ACTION OF BARBITURATES IN VIVO

Aldridge and Parker (1960) using suspensions of liver mitochondria demonstrated with oxybarbiturates an inhibition of respiration without uncoupling oxidative phosphorylation. This was in contrast to the views expressed by Brody and Bain (1954) who suggested that the mode of action of the barbiturates on the C.N.S. was mediated by an uncoupling of oxidative phosphorylation.

Aldridge and Parker further showed that the use of succinate as substrate for the mitochondrial suspension abolished the inhibition of respiration caused by the oxybarbiturate and suggested therefore that the site of action of the oxybarbiturate was at some stage before the entry of succinate into the oxidative chain. Succinate is known to enter the oxidative site at a point after the pyridine nucleotide stage and hence the site of action of barbiturate was proposed to be at the oxidation of pyridine nucleotide.



Chance and Hollinger (1963), again using an isolated system of liver mitochondria, identified the precise site of action as being between pyridine nucleotide and cytochrome b.

In view of this work on isolated systems it was decided to test the validity of the proposed site of action of barbiturate in vivo by the effect of sleeping time caused by amylobarbiturate in rats with or without treatment with sodium succinate.

The succinate was administered in 1M conc. in small quantities (15 μL) into the right ventricle of the rat's brain using specially prepared needles. This obviated any effect caused by systemic metabolism of succinate or delayed passage across the "blood brain barrier".

The rats (140-160g) were fasted overnight before all experiments in an attempt to standardize conditions as much as possible.

SLEEPING TIMES

Results show that intraventricular injection of this small amount of succinate reduced the sleeping time of rats to about one-third of that of controls given either pruvate (1M) or NaCl. (2M). (Pyruvate was given as control because (a) it is also a metabolizable intermediate, and (b) should not affect sleeping time from normal with barbiturate anaesthesia since it enters the oxidative process before the proposed site of barbiturate block. The latter was shown to be true.)

The difference between mean sleeping time of control (pyruvate group) and succinate treated group of rats was statistically highly significant.

BLOOD LEVELS

A standard spectrophotometric method for the estimation of blood barbiturate level was adapted to a micro method which gave reproducible results which obey Beer's law.

The results showed that blood barbiturate levels measured at the time of waking from anaesthesia in succinate treated rats were statistically significantly higher than in pyruvate treated controls. These results suggest that the effect of succinate was not mediated through an increase in barbiturate metabolism thereby leading to a decrease in blood level since succinate treated rats awoke with blood barbiturate level inconsistent with consciousness in control rats. As a further control, blood and brain levels were estimated for the same rats and a good correlation was shown to exist, showing that blood barbiturate levels accurately represent brain barbiturate levels.

DISCUSSION

The results confirm the in vitro findings of Chain and Hollinger (1963) on isolated liver mitchondria and extend their conclusions to cover brain *in vivo*.

The present results give a very good indication that the pharmacological action of the oxybarbiturates in the intact animals is identical to that indicated by the biochemical experiments in vitro. The fact that succinate has such a marked antagonistic action to the barbiturates in contrast to pyruvate indicates that metabolism of the former substrate by-passes the site of action of the oxybarbiturates.

JOHN WALLWORK, B.Sc. (Hons.)

ACKNOWLEDGMENTS

I would like to express my thanks to Professor Perry and the Department of Pharmacology for all the help they have given; also the M.R.C. Unit for Research in Brain Metabolism, in particular Dr. H. W. Reading in whose laboratory and under whose guidance this work was carried out.

REFERENCES

ALDRIDGE & PARKER 1960. Biochem. J. 76, 47.

BRODY & BAIN 1954. J. Pharm. Exp. Ther. 110, 148.

CHAIN & HOLLINGER 1963. J. Biol. Chem. 278, 419.

DIAGNOSTIC PROBLEM

(from page 33)

Diagnosis:

Retroperitoneal bleeding from oesophageal varices produced by alcoholic cirrhosis.

THE CONTRIBUTORS

PROFESSOR RONALD GIRDWOOD *is head of the University Department of Therapeutics at the Royal Infirmary, Edinburgh. It is most appropriate that he should continue the series of articles in* RES MEDICA *concerned with the examination of the various systems of the human body for he is a renowned authority in his field and is well known to Edinburgh medical students for his lectures and contributions to recognised text books.*

DR. GEORGE ASHCROFT *is the Assistant Director of the Unit for Research in Brain Metabolism in the Pharmacology Department. His article, from a lecture given to the Society last year, describes the exciting but complex features involved in attempting a biochemical elucidation of depressive illness.*

DR. W. R. M. ALEXANDER *is a consultant physician at the Northern General Hospital. His research interests lie in the field of immunity reactions in relation to rheumatic diseases, a field that has generated much excitement over the past few years.*

DAVID MCLEOD *is a first class honours graduate in physiology and a Junior President of the Society. His interest in Sir James Mackenzie stems from his ties with Burnley and his article complements an earlier account of Mackenzie in this Journal.*

JOHN WALLWORK *is an honours graduate in Pharmacology and last summer conducted research on the action of Barbiturates. Those who work on an undergraduate vacation research grant are encouraged to submit a precis of their findings to the Journal.*

BOOK REVIEWS

Notes On Medical Virology by Morag C. Tinbury. Published by E. & S. Livingstone Ltd., Edinburgh 1967.

This short book commences by discussing the general properties of viruses and their laboratory diagnosis, going on to discuss each group of viruses and the disease associated with them in turn. At the end there are short chapters on viruses and tumours and the rickettsiae.

As its title implies it is written in note form but at the same time is eminently readable and covers the topic in sufficient detail for the Student or Medical Practitioner. It is a book which ought to find a place on ever doctor's bookshelf.

C.J.E.

Racial And Geographical Factors In Tumour Incidence (University of Edinburgh Press — Pfizer Medical). Monograph No. 2. Edited by A. A. Shivas. 63s.

This very well-produced book is a record of an interesting conference held in Edinburgh in 1966. The title does not do complete justice to the contents because other factors influencing malignancy besides racial and geographical ones were considered and discussed at this meeting, and are reported in this book.

The standard of contributions is uniformly high and all gain from a more leisurely perusal than was possible when they were originally presented. It is probably unfair to single out for special mention any particular contribution but both the paper and the closing remarks by Ernest L. Wynder are more than ordinarily interesting; the closing remarks could be called provocative. This reviewer's only critical comment is that the book might have been better if the contents were more fully indexed; the discussion which followed several papers could also have been included with benefit.

J.M.L.

Psychiatric Disorders Of Obstetrics by A. A. Baker. Blackwell Scientific Publications. 27s 6d.

This book reads easily and will be a boon to any medical student, especially those interested in the field. The approach is one of suggestion rather than dogmatism, so that the reader is stimulated to think. The text is sprinkled generously with case histories and Dr. Baker continually stresses the importance of treating the patient in relation to her environment rather than treating the disorder empirically.

The first four chapters provide valuable elucidation of the emotional changes that are liable to take place in the pregnant female, while the final chapter on termination of pregnancy and sterilisation is of special relevance owing to the new law relating to abortion. The author stresses the importance of considering these latter topics individually; however he is again not dogmatic, and this lends weight to the argument that when dealing with this kind of situation one is not dealing with clearcut issues.

The book is heartily recommended to all students, medical and nonmedical.

D.J.H.

A Synopsis of Children's Diseases (4th Edition) by Rendle-Short & Gray. John Wright & Sons Ltd., Bristol, 52s 6d.

This book provides a comprehensive coverage of the common and the rare in childhood illnesses. A commendable feature is the inclusion of references to the newer syndromes, so that the reader may conveniently augment his reading in areas of interest. The layout is clear and emphasises classification and methodology of approach. Hence it is well suited to the needs of the examinee if he can afford the cost.

M.F.M.

Biochemical Values In Clinical Medicine by Robert Eastham. John Wright & Sons Ltd., Bristol. 15s.

The main attraction of this little book is that it is small enough for the pocket, and hence readily available for ward rounds and so on. Not only values but also tests in common use are included in the book, and recent extensive revision has ensured that the procedures are up-to-date. The presentation is neat and there is an efficient index at the back for those caught out by a consultant's question.

M.F.M.

Roxburgh's Common Skin Diseases (13th Edition) by Peter Borrie. H. K. Lewis & Co. Ltd. £2 10s.

This is an excellent book, written in a pleasant style. As a study of common, and hence relevant skin diseases, it succeeds in avoiding the dryness of a concise textbook and the verbosity of a more comprehensive one. Each skin condition is clearly defined and classified in a logical sequence, so that a definite pattern emerges. Other notable features include many excellent illustrations and the attention paid to practical details of treatment.

In conclusion, this book is recommended to all students and is a "must" for the future G.P.

J.M.D.

A New Look At Industrial Medicine by R. L. Luffingham. Pitman Medical 12s 6d.

The author of this the latest in the New Look series is a Medical Officer to the British Transport Docks Board. He writes with dismay on the shortcomings of present day industrial medicine. Determinedly propounding the view that this is an area in which effective preventive medicine may be practised he explores the changes possible and visualises an Occupational Health Service on a par with the Hospital and General Practitioner branches. He wishes to persuade industry that the maintenance of the health of the employee is as important as the regular care of expensive plant. He stresses the error that the industrial medical officer makes in attempting to provide management with a faultless casualty service, thus apparently denying the feasibility of the more exhausting but more worthwhile preventive service.

Proposals for changes in the factory doctor service are cogently presented, but the concept of an Occupational Health Service seems shaky. Clerical and distributive workers would be difficult to cover within the suggested framework.

Enthusiastically written the book suffers somewhat from contemporary political jargon; nevertheless it shows a valuable originality of thought on a neglected aspect of medicine.

W.L.C.

Cervical Spondylosis edited by Lord Brain & Marcia Wilkinson. William Heinemann Ltd. 55s.

Cervical spondylosis, hardly recognised twenty years ago, is subjected to careful scrutiny in this book. The anatomy, pathology, symptomatology, radiology and clinical aspects of the condition are expertly reviewed, aided by copious photographs and line drawings of a high standard. For those concerned with the subject this comprehensive volume will be invaluable, and it is within scope of the interested student, clinically and financially.

M.F.M.

Diseases Of The Nose, Throat And Ear (8th Ed.) by Hall & Coleman. Livingstone 30s.

A concise but comprehensive study of the most common ENT diseases. Both the relevant facts and considerable detail have been crammed into small bulk and an economic price. The result is a useful practical handbook for the practitioner, but rather heavy reading for the student approaching ENT for the first time — especially as this concentration of facts leads to an uninteresting style.

Illustrations, though sparse in places, are fairly good and methods of treatment are clearly described. The book is recommended to all with more than a superficial interest in ENT diseases.

J.M.D.

The Vesico-Vaginal Fistula by J. Chassar Moir. Bailliere Tindall & Cassell Ltd. 60s.

The subject of this book is beyond the scope of the undergraduate. Thanks to the great improvement in the standard of obstetrics now practised in this country the disorder is relatively uncommon. Nevertheless it is as well to be aware of this distressing condition as it is remediable.

In the first chapter the author gives a lucid account of the history of the treatment of the condition, including a full account of the life of J. Marion Sims. The remainder of the book requires a knowledge of surgical technique for useful appreciation. This limits its value for the medical student but ensures its importance to those interested in the speciality.

D.J.H.

JOURNAL

of the

ROYAL COLLEGE

of

SURGEONS

of

EDINBURGH

Published Bimonthly: January, March, May, July, September, November

Annual Subscription: 50s. *post free*

Editor: Sir JOHN BRUCE, C.B.E., T.D., F.R.C.S.E., F.R.S.E.

Printed for McKenzie & Arthur (Publications) Ltd., George Street, Edinburgh, by The Galloway Gazette Press, Newton Stewart, Wigtownshire, Scotland.