CLINICAL PATHOLOGY IN GENERAL PRACTICE

TROPICAL DISEASES IN BRITAIN

BY

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The problems most commonly confronting the practitioner dealing with patients who have returned from the Tropics are those concerning the investigation of fevers and alimentary upsets. The possible causes of the illness, and therefore the way in which the investigation is conducted, depend to a considerable extent on the time which has elapsed since leaving the Tropics. Thus air travel enables patients to be first seen at the onset of tropical infections with short incubation periods such as primary malaria, sandfly fever, dengue, yellow fever, rickettsial fevers, and bacillary dysentery. Among those falling ill after arrival in this country by sea, malarial relapses, dysentery, enteric fevers, and kala-azar have been most commonly found. Diseases in which the incubation period is long are, however, as likely to occur among those travelling by air as they are in those travelling by sea. Air travel merely adds to the list of diseases it is possible to encounter by reducing the time elapsing between leaving the Tropics and arriving in this country.

Malaria

Malaria is the commonest cause of fever in those who have visited endemic areas less than 18 months before the onset of their symptoms. Awareness of the possibility of the infection is the first step towards its diagnosis, and light might be thrown on many diagnostic problems besides that presented by malaria if an inquiry into the patient's recent movements were made in all cases in which such information is not already known to the practitioner. The two commonest forms of malaria are malignant tertian, caused by *Plasmodium falciparum*, and benign tertian, caused by *P. vivax*. It is important to keep the former in mind, especially with patients who have very recently visited tropical Africa, as unless this infection is promptly diagnosed and treated grave illness with cerebral complications and possibly a fatal outcome may result. Infections with *P. vivax* are more commonly encountered among patients who have lived in the Middle or Far East, and latterly have constituted a special problem in soldiers returning from Korea. In these the possibility of malaria is commonly overlooked, as there may be no history of a primary attack in the endemic region, this having been adequately suppressed by the routine administration of antimalarial drugs. Such patients may have chronic ill-health until the infection is adequately treated. It is important to stress that if *P. falciparum* infections are similarly overlooked the result is usually much more serious.

The Search for Malarial Parasites

In cases in which malaria is suspected, the most important investigation is examination of one or more blood films, and these should invariably be made before treatment is started. Whether they are thought to show or to fail to show parasites they should be retained for possible further examination, as mistakes may be made by platelets or artifacts being confused with parasites. To prepare a blood film is one of the simplest medical procedures, yet it is amazing how seldom it is done well. Microscope slides must first be rendered grease-free, and for this a good method is by washing with "monkey brand" or similar

soap, soaking in alcohol, and flaming. A spreader is made by breaking off the corners of a slide after scratching with a diamond. The lobe of an ear or the tip of a finger is then cleaned with spirit or ether. The lobe of the ear is to be preferred to a finger, as it is not only less sensitive to pain than the finger but is also less exposed to infection. Ether is perhaps best for cleaning the skin, as its use reduces the possibility of grease interfering with the spreading of the film. Hypodermic needles are unsuitable for puncturing the skin, for the drop of blood obtained is often too small to make a satisfactory film. A special skin-puncturing needle or, if none is available, a large-sized venepuncturing needle is more satisfactory. A sharp jab causes less discomfort to the patient than a wound made slowly and hesitantly.

Thick and thin preparations should be made, the former by using a pin to smear the drop of blood on the slide over a circular area of approximately $\frac{1}{2}$ in. (12 mm.) in diameter, the latter by spreading the drop with the spreader already prepared. The drop is placed at one end of the slide and allowed to run across the width of the spreader, which is held at an angle of 45 degrees and pushed along the length of the slide. Thick preparations must be allowed to dry thoroughly for 20–30 minutes. Their contained blood is then laked in an aqueous solution of 2% formalin and 1% glacial acetic acid. They are washed in distilled water and stained with dilute Giemsa stain, one drop being added to 1 ml. of distilled water and allowed to remain on the slide for 20–30 minutes before being poured off, and the slide allowed to dry without heating or blotting.

If large numbers of slides are to be stained, Field's method is conveniently rapid and labour-saving. For this a solvent is made by dissolving 10 g. of anhydrous disodium hydrogen phosphate and 12.5 g. of anhydrous potassium dihydrogen phosphate in 1 litre of distilled water. Solution A is prepared by dissolving 0.8 g. of powdered methylene blue and 0.5 g. of azure I in 500 ml. of the solvent. Solution B is prepared by dissolving 1 g. of yellow eosin in 500 ml. of solvent and filtering. Films are stained by immersing in solution A for one to three seconds, rinsing for five seconds in tap-water or in solvent, immersing for one to three seconds in solution B, and washing for three seconds in tap-water. They are then allowed to dry. In using this method films are not fixed and care is therefore necessary in handling them lest they become detached from the slide.

Thin films are most conveniently and satisfactorily stained with Leishman's stain. The slide is covered with undiluted stain, the number of drops required being noted, and after 10 seconds three times this volume of distilled water of pH 7.2 is added. This pH is obtained by adding lithium carbonate to the water till an aliquot gives a yellow reaction with bromthymol blue. The slide is stained with the diluted stain for 30 minutes and then flushed with the distilled water of pH 7.2 and allowed to dry. This method has the advantage of showing up well the Schüffner dots in cells infected with *P. vivax*.

A description of the various malarial parasites is outside the scope of this article, and for that the reader is referred to the standard works on tropical medicine and parasitology. It should, however, be mentioned that, unless parasites are being searched for frequently, errors, even by trained pathologists, are not uncommon. Perhaps the commonest is to regard an artifact as a parasite; less commonly, parasites when scanty are overlooked.

It is often questioned whether antimalarial treatment should be begun before a definitive diagnosis has been

made. There can be no doubt that falciparum malaria in non-immune subjects, if not promptly treated, may give rise to severe and even fatal illness. Thus when it is considered that possible delay in treatment would be dangerous and the blood cannot be examined promptly, it is best to start treatment, though blood films should be made for later examination and confirmation of the diagnosis. To give treatment without awaiting the report on, or making a personal examination of, a blood film may be a method of managing cases in emergency, but it is not a method of diagnosis. If the temperature comes down following treatment in such cases, it is unwise to deduce that malaria was the cause of the fever unless confirmation of the diagnosis is ultimately obtained from examination of blood films. Therapeutic diagnoses of this kind are associated with innumerable pitfalls, and such slipshod methods are harmful alike to the patient and to the profession.

Investigation of Non-malarial Fevers

Non-malarial causes of fever in persons recently returned from the Tropics include bacterial diseases such as bacillary dysentery, typhoid and paratyphoid fevers, brucellosis, tuberculosis, urinary infections, and tonsillitis; protozoal infections such as kala-azar (visceral leishmaniasis), trypanosomiasis, amoebic dysentery, and amoebic liver abscess; and virus infections including the common cold and its upper respiratory complications, especially maxillary sinus infection, influenza, and rarely sandfly and dengue fevers. Typhus and psittacosis are occasionally encountered. These may be confused with malaria, and patients with them have at various times been sent to the Hospital for Tropical Diseases in London diagnosed as cases of malaria. In some such cases slides have been recovered in which artifacts or platelets have been shown to have been wrongly mistaken for parasites. In others no slides had been examined before admission to hospital, but it is remarkable that even so not uncommonly the diagnosis of malaria had been regarded as so incontrovertible that the malaria was said to be of a type insensitive to the drug used. In the Tropics, where the disease is commoner and laboratories may be lacking, or overburdened with work, such errors are more often made. They are responsible for many of the false notions regarding the efficacy of anti-malarial drugs which from time to time become widely held.

The investigation of patients presenting with symptoms suggesting dysentery is discussed below. Tests which may help to differentiate malaria and urinary and respiratory infections from the other causes of fever mentioned include the white blood cell count. This should be carried out as a routine; it is usually low in enteric fevers, brucellosis, kala-azar, and sandfly and dengue fevers, and a differential count shows a reduction in the proportion of polymorphonuclear cells. The urine and the deposit obtained from it after centrifuging should be examined microscopically for pus cells and cultured if any are found. In males mid-stream specimens of urine collected after cleansing the glands may be used for the purpose, in females a catheter specimen is essential. A radiograph of the chest should be taken in all cases in which the cause of the fever is not apparent, even if there are no symptoms or signs referable to the chest.

In cases in which the diagnosis does not become clear as a result of these investigations enteric fever, brucellosis, and typhus must be considered, and blood should be collected for culture, for enteric and brucella agglutination tests, and for the Weil-Felix reaction. For the cultural investigations 5 ml. of blood is added to 100 ml. of broth containing 0.5% sodium taurocholate, and a second 5-ml. sample is added to 100 ml. of plain broth. In taking the blood it is advisable to use a dry sterilized syringe; boiling should be relied upon only in emergencies. It is commonly said that for positive cultural results in enteric fever blood must be taken within the first few days of the attack. This, however, is not strictly true; the chances of obtaining a

positive culture at that time are greater than they are later, but positive results may be obtained at any stage in the illness and it is never sound practice to omit this investigation. It is important to inoculate the broth with the blood as soon as it is withdrawn from the vein and to transfer the specimen to an incubator with the minimum of delay. Where brucellosis is suspected the fact should be clearly stated, as cultures should then be incubated in air containing 10% carbon dioxide, for in primary culture *Brucella abortus* will often grow only under increased CO₂ tension. *Br. melitensis* and *Br. suis* will, however, grow satisfactorily in atmospheric air.

Blood for the Widal and brucella agglutination tests and for the Weil-Felix reaction should be collected in a dry sterile syringe and allowed to clot in a dry sterile tube or screw-capped bottle. If the journey to the laboratory is one occupying more than an hour or two, the serum should be pipetted off the blood clot and sent in a sterile screw-topped container or in a sealed glass ampoule.

Kala-azar should be suspected especially in those chronically or intermittently febrile and who have hepatosplenomegaly without marked prostration. Isolation of the causal parasite, *Leishmania donovani*, is the only satisfactory way of making a diagnosis, and it should first be searched for in blood films. In these, however, parasites are invariably scanty; they are more numerous in films of sternal marrow. In making the films it is important for the microscope slides to be absolutely dry, otherwise the parasites will be damaged and may not be recognizable. If examination of blood and marrow films gives negative results, blood should be cultured on N.N.N. (Nicolle, Nory, and MacNeal), Adler's, or Lourie's medium. On these media blood is sown in single drops, and great care must be taken to exclude secondary bacterial infection. The culture is kept at 28° C. and growth is to be expected within three weeks. Material in which *L. donovani* can be found may also be obtained by splenic puncture, but this procedure is best carried out only in hospital and by those trained in the technique. The formol-gel and antimony, or Chopra, tests are useful guides to the diagnosis of kala-azar. These tests are positive when serum globulins are increased, but as this occurs in several other diseases they are not specific. The formol-gel test is carried out by adding a drop of commercial formalin to 1 ml. of the patient's serum, which in positive cases becomes opaque and sets into a gel in 10-30 minutes. In the Chopra test a few drops of a 4% solution of any pentavalent antimony compound are added to a 10% solution of the patient's serum in distilled water. In positive cases the mixture becomes opaque in a few minutes.

Alimentary Disorders

In patients recently returned from the Tropics and presenting with symptoms referable to the alimentary system the most common causes are amoebic dysentery, amoebic hepatitis, amoebic abscess of the liver, and a functional or nervous upset. Less common causes include bacillary dysentery, schistosomiasis, ulcerative colitis, and neoplasms of the bowel wall.

Dysentery

Examination of the stools macroscopically and microscopically will do more to elucidate the diagnosis than any other tests. Thus in bacillary dysentery blood, mucus, or a purulent cellular exudate will be found; in amoebic dysentery exudate is less abundant, the specimen more faeculent, and *Entamoeba histolytica* or its cysts are present. In functional or nervous alimentary upsets the stool may be fluid, semi-formed, or formed—it is not uncommon for several small formed stools to be passed daily. Intestinal spasm may cause the stools to be ribbon-shaped. In such cases there is often an excessive amount of mucus, and sometimes this is passed as casts of the intestinal wall or in long strings.

There is often disagreement on the number of stools which should be examined before a diagnosis of amoebic dysentery

is excluded. Wenyon and O'Connor have said, "If *E. histolytica* are giving trouble, the probability is that amoebae or their cysts will be found at once." Their experience is similar to that of most others practising tropical medicine. Much depends on the skill and experience of the person examining the specimens; if he is fully conversant with the appearance of the parasite and is practised in stool examination, a series of six specimens is usually regarded as sufficient. It should be stressed that, unless a person is examining such specimens frequently, he is liable to commit errors in identification of parasites and objects resembling them, and in view of this it is highly desirable that these investigations should be carried out at a centre established for the purpose. Some advocate that stools should be collected after saline purgation, but the consensus is that purgation does not increase the chances of finding amoebae or cysts; there is also the possibility that salines may destroy amoebae by their osmotic effect.

Cultural methods of isolating amoebae are not recommended for routine use, as it is not uncommon for cultures to be negative even when stools are known to contain the amoebae. Various concentration techniques increase the chances of finding cysts in a specimen, but these methods are not suitable for the isolation of vegetative amoebae, as the latter are destroyed by the solution of zinc sulphate or other salt used in the process. Some state that the chances of finding amoebae or cysts are increased by giving the patient one or two doses of emetine by injection. But no reliable evidence of the effectiveness of this so-called provocative emetine has ever been put forward. It seems probable that such popularity as the method obtained was based on confusion with the use of provocative arsenic in syphilis. Each specimen should be collected in a dry bedpan at room temperature, as parasites may be damaged by undue warmth or by water which sometimes remains in bedpans after they have been washed. When collecting faeces for examination it is important to warn the patient not to micturate into the container into which the faeces are being passed.

Vegetative forms of *E. histolytica* become immobile and disintegrate within a few hours; thus any examination for them must be carried out as quickly as possible. Nevertheless, undue emphasis is sometimes placed on this point. There is certainly no truth in the oft-stated belief that if a specimen cannot be examined immediately it should be kept warm to preserve motility of the amoebae. The reverse is in fact true, for if they are kept cool they remain alive much longer than if kept warm. When chilled, amoebic trophozoites lose their motility, but this rapidly returns when they are again brought up to body temperature. Amoebic cysts remain identifiable for several days in faeces kept in a closed container at room temperature.

In the diagnosis of amoebic dysentery the complement-fixation test is as yet completely unreliable; the same can also be said of barium enemata and other radiological procedures. Sigmoidoscopy is occasionally helpful, but it is remarkable how seldom it affords positive evidence of the disease in cases in which the diagnosis has not already been proved by stool examination. It is, of course, of great value in distinguishing ulcerative colitis or neoplasms of the bowel from dysentery, and negative sigmoidoscopic findings also assist in excluding organic disease. An increasing number of observers are becoming sceptical of small pits in the bowel mucosa as evidence of previous amoebic infection. These received much publicity towards the end of the second world war and were supposed to be the scars of amoebic ulcers. Such ulcers, however, unless of great size, normally heal and their scars completely disappear. In this respect they are similar to abrasions and ulcers of other mucous surfaces and parts of the body. It is probable that many of the depressions to which attention was drawn were the mouths of mucous glands normally present in the rectum and colon.

Thus, in dysentery, the most valuable diagnostic procedure remains the examination of a series of specimens of faeces

and particularly of any blood or mucus adherent to or intermingled with such specimens. The specimens are best collected without purgation or the use of provocative emetine.

Amoebic Hepatitis and Liver Abscess

Amoebic hepatitis is usually an accompaniment of an acute attack of amoebic dysentery; its presence is indicated by pain and tenderness in and enlargement of the liver, by leucocytosis, and sometimes by pain in the right shoulder. Acute hepatitis of this kind usually settles down satisfactorily with adequate anti-amoebic treatment and is seldom difficult to diagnose. An amoebic abscess of the liver may, however, cause a more complicated diagnostic problem. Months or years may elapse between the time of the original infection and that at which the first symptoms develop. In some patients there may be no antecedent history of amoebic dysentery, the bowel infection having been subclinical or mild and regarded as transient enteritis only. In the diagnosis of amoebic liver abscess the investigations of greatest value are screening of the liver and diaphragmatic areas, the white blood cell and differential counts, and aspiration of the abscess contents. Stool examination usually gives negative results, for by the time the abscess has developed the original alimentary infection has in most cases been adequately treated or resolved spontaneously. In such cases radiological screen examination usually shows elevation and paradoxical movement of the right diaphragm on respiration. There may also be collapse or patchy consolidation of the base of the right lung. A moderate leucocytosis is usual with some increase of the polymorphonuclear cells, though this is by no means invariable and cases occur in which the white blood cell and differential counts depart but little from normal.

If the clinical picture and/or radiological appearances suggest that a collection of pus is present in the right lobe of the liver, a diagnostic aspiration should be carried out. Aspiration of the left lobe of the liver should not be attempted, as it cannot be reached other than by open operation without incurring risk of damaging vital structures. The right lobe is best aspirated with a large-bore needle introduced in the right mid-axillary line in the ninth or tenth intercostal space or in the right scapular line in the eleventh intercostal space. Any pus obtained should be examined microscopically and cultured. Amoebae are only rarely obtained in such pus, as they live in the abscess wall. Unless there has been secondary infection the pus is sterile on culture. In cases in which it is not infected it is of the same colour as the liver and is commonly likened to anchovy sauce. When infected it has a greenish or yellowish tint.

Schistosomiasis

When schistosomiasis is suspected examination of both urine and faeces is important. Ova of *Schistosoma mansoni* are most commonly found in the faeces or in material removed by biopsy of the rectal wall. Ova of *S. haematobium* are more numerous in the urine though they may be found in the faeces or in rectal mucosa. It is in the last few drops of urine expressed during micturition that the eggs of *S. haematobium* are most numerous. If examination of such a specimen reveals no eggs a 24-hour collection of urine should be allowed to sediment, three-quarters of the collection is then siphoned off and the remainder centrifuged and examined microscopically. In schistosomiasis the differential white blood cell count often shows an eosinophilia. At the Hospital for Tropical Diseases, London, a complement-fixation test for schistosomiasis can be done and this gives reliable results.

Conclusion

The diagnosis in most tropical diseases can be reached by carrying out simple laboratory procedures often involving the use of little more than the microscope, but the interpretation of results and the recognition of the various parasites and or the structures and artifacts which may simulate them call for considerable training and experience. The late effects of errors in interpretation and consequent

mismanagement are not uncommonly encountered at the various tropical centres in Great Britain, and such mismanagement may lead to chronic ill-health and in some cases even to the death of the patient. It is therefore in the patients' interest that whenever possible they should be investigated in a centre for tropical diseases. Apart from various military establishments there are three of these in Great Britain—namely, the Hospital for Tropical Diseases, 4, St. Pancras Way, London, N.W.1.; the School of Tropical Medicine, Pembroke Place, Liverpool; and the Tropical Diseases Unit, Eastern General Hospital, Edinburgh.

Next article on Clinical Pathology.—"Pituitary Function," by Dr. G. A. Smart.

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MEDICAL ART

[FROM A SPECIAL CORRESPONDENT]

Gaiety once again is the keynote of the exhibition¹ of work by members of the Medical Art Society. Nearly all the paintings evade the criticism of much contemporary art that it cannot be lived with; indeed, any of these would lend distinction to the kind of rooms that most of us are condemned to inhabit. But if the gay spontaneity of this work betokens the amateur, the technique often suggests a more practised hand. Mr. Elliott Blake's impressionist oil painting of autumn leaves in a Sussex lane (No. 23) catches the eye immediately as a fine piece of painting, though the composition is somewhat precisely balanced. Another plastic surgeon, Sir Harold Gillies, also enchants the eye with a landscape of winter, "Beech Trees in Snow" (No. 20). Dr. A. B. Hewlett, as usual, contributes one of the outstanding paintings of the show, "The Upper Reaches" (No. 42), a beautiful evocation in his highly distinctive style of a typical corner of the English countryside. "The Edge of the Downs" (No. 64), by Dr. G. M. Archer, is also a most successful landscape; though more conventional in technique, it glows with unusual warmth of feeling. Other pictures in this room that should not be missed include the two negroid heads by Dr. W. Hartston (Nos. 2 and 6), "Summer Mist" (No. 26) by Dr. E. P. Scott, and "The Reef" (No. 54) by Dr. A. G. Duncan.

Few of these week-end painters—or of any amateur painters in this country—owe much of their technique to any of the artistic movements that succeeded the Impressionists. However, Mr. R. T. Payne shows some fanciful abstractions, attached to rather than illustrating texts from Genesis; Mr. W. M. Van Essen has evidently had an encounter (No. 111), not altogether fruitless, with Picasso; and Mr. Geoffrey Parker's "Bruges" (No. 89), misprinted in the catalogue, suggests some affinity with the German expressionist movement of the 'twenties. Dr. H. Hales's *jeu d'esprit* in wire (No. 80) belongs more to the realm of doodling than of art, but it is an amusing contrivance all the same. On the opposite wall near by is a particularly colourful and decorative painting by Lady Whitby, "Dahlia's" (No. 98). Here we are back with the Impressionists again, and it is an easy step to Dr. Joy Patrick's striking portrait of "Cecilia" (No. 107).

Among the water-colours Dr. A. E. O'Donnell shows an excellent snow scene that yet communicates a feeling of

warmth derived from the pleasure of painting it. Mr. Holmes Sellors catches the passer's eye with some gay scenes (Nos. 183 and 184), and Dr. Reginald Morshead has recorded Sussex's "Chanctonbury" (No. 171) in a refreshingly cool study. In this same room is a beautiful piece of sculpture by Dr. Geoffrey Konstam, a head of a baby (No. 141). This exquisite work deserves long contemplation.

The president of the society, Sir Philip Manson-Bahr, himself contributes several paintings, in No. 9 giving an agreeable portrait of his horse, and in No. 150 bringing to Sussex an eye that seems to have been averted only momentarily from tropic climes. He and the members of the society deserve our thanks as well as our congratulations for putting on this exhibition of such enchanting talent.

THE CHANGING AND THE UNCHANGING FACE OF MEDICINE

FIRST SYDNEY BODY LECTURE BY
Sir FRANCIS WALSHE, F.R.S.

The first lecture under the Sydney Body Trust was delivered at Southend-on-Sea Hospital, Rochford, on April 14 by Sir Francis Walshe. This Trust has recently been instituted under a benefaction by Mr. Sydney Body, M.P.S., to provide for a lecture to be given every year designed to promote sympathetic understanding between the medical profession and the public; also a gold medal to be awarded, not necessarily annually, to a medical man or woman for outstanding merit in some field of research or achievement.

Sir FRANCIS WALSHE addressed a large and distinguished audience on "The Changing and Unchanging Face of Medicine." Medicine, he said, was the oldest learned profession in the world, and each successive generation of doctors stood on the shoulders of its predecessors. During the forty years of his own professional life medicine had undergone vast changes, but equally there were aspects of it which had not and would not change.

When he started medicine there was no scientific chemotherapy as they now saw it. Patients suffering from pernicious anaemia survived for about four years, and nothing could check the ruthless course of their malady. Surgery of the lung, the heart, and the brain had developed during his lifetime. The triumphs of a sepsis, anaesthesia, and post-operative care had transformed the surgical operation. Preventive medicine had advanced out of all knowledge. The men of his generation in medicine had been privileged to live in an era of more rapid advance than anything the previous history of medicine had seen.

At the same time he looked back occasionally on the doctor of 40 years ago, and realized how often he had possessed that clinical judgment without which none of the modern techniques could be used to full advantage. These modern resources were two-edged weapons, and it was easy for zeal to outrun discretion.

The Impact of the Health Service

Since the introduction of the National Health Service, Sir Francis Walshe continued, many people seemed to have developed an attitude of helplessness concerning their own and their children's health. In former days if a child fell down and grazed his shin his mother bathed it and put on a plaster, but to-day he was sent to join the queue at the surgery. "After all, why do what the doctor is paid to do? We pay for welfare; why should we not have it?"

Doctors were only human beings: they had their private lives, their foibles, too; they sometimes made mistakes. It was not unknown for them to make errors of judgment

¹At Walker's Galleries, Bond Street, London, W.1, until May 8. Open 10 a.m. to 5 p.m., Saturdays 10 a.m. to 1 p.m.