THE DIFFERENTIAL DIAGNOSIS OF PROLONGED PYREXIA IN INDIA.

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In the medical wards of a military hospital in India there are many difficult problems to harass the medical officer in charge, and one of the most difficult and worrying is the diagnosis of a case of prolonged pyrexia. There is nothing more disheartening than to watch one of these cases from day to day, while, even after enlisting all the aids, both clinical and laboratory, at one's command, the diagnosis remains elusive. I feel, therefore, that it might be of some help to young officers who are about to commence a tour of duty in India if I attempt, in this short article, to describe some points which might help in the differential diagnosis of these "fevers." I shall deal only with cases in which the pyrexia exceeds seven days, and in which there is no obvious cause, such as a large subcutaneous abscess, or lobar pneumonia.

In the investigation of these fevers, a very careful clinical examination is the first essential. There are so many cases in which physical signs are few, or absent, that examination is apt to become perfunctory, and some vital point is missed. After a careful examination, the blood is examined for parasites; blood cultures, Widals and blood counts are made, and the patient is sent for X-ray examination, if this is considered necessary.

The total and differential white blood counts must be done accurately if they are going to be of any help. It is far better to do without this aid to diagnosis, if the result cannot be depended upon. An inaccurate result may mean a wrong diagnosis. The normal total white count varies between 6,000 and 9,000 cells per cubic millimetre, and the average differential count is: Polynuclear leucocytes 64 to 68 per cent; lymphocytes (large and small) 30 to 34 per cent; large mononuclears 2 to 4 per cent; eosinophils 1 per cent.

In any "fever" occurring in India malaria is the first disease to exclude, and blood smears are examined from day to day. If these, after careful examination, show no malaria parasites, and the patient has taken no antimalaria drug, then, in the great majority of cases, the disease is not malaria. There is one exception to this.

A malignant tertian infection may cause a continued fever with no obvious intermittent paroxysms, and the parasite may be very difficult to find. The spleen is enlarged, the patient complains of continuous headache, and the clinical picture closely resembles an enteric group infection. The following points may be of some assistance in diagnosing these cases.
The cases usually occur during the second half of the malaria season, when malignant tertian infections are prevalent, and there may be associated cases, in whose blood the parasite has been found. If they are watched carefully and questioned about their symptoms, it will commonly be found that the headache increases in severity towards the end of the morning, or in the afternoon, and there may be a very slight rigor. Eventually, after a number of examinations, the small ring form of the malignant tertian parasite is found in the blood smear, and the diagnosis is established. The spleen is not palpable in every case of malaria, and this applies especially to the primary attacks.

There is one fairly common condition which sometimes resembles malaria, and now and again cases are diagnosed as clinical malaria. This is a Bacillus coli infection, which may occur in paroxysms resembling malaria rigors, or as a continued pyrexia.

There may be no symptoms referable to the urinary tract, and the urine may show nothing abnormal on microscopical examination, but if a catheter specimen is sent for culture a pure growth of B. coli is isolated. It is difficult to isolate this organism from the blood. This disease is not uncommon in young soldiers, and should be kept in mind when other examinations are negative.

Relapsing fever and rat bite fever are two conditions which are usually treated as malaria, until their respective organisms are discovered. These diseases are not commonly met with in Army practice in India, but in a case which defeats diagnosis they must be kept in mind.

Relapsing fever, as its name implies, occurs in paroxysms, with apyrexial intervals, and the number of relapses varies. There are no characteristic signs or symptoms, but if the blood is carefully examined the Treponema recurrentis will be found.

In rat bite fever the symptoms are somewhat similar, but there is usually the history of a rat bite, and the old wound flares up with each paroxysm, while the lymphatic glands draining the area become inflamed and enlarged. The Spirillum minus is difficult to find in the peripheral blood, which should be inoculated into white rats or mice.

Enteric group infection is the next problem in diagnosis and this may prove a very difficult one.

The textbook picture of typhoid fever, with the step-ladder rise in temperature, the enlarged spleen, the typical rash, the tympanitic abdomen and "pea soup" stools is not commonly seen nowadays in an inoculated community like the Army. Most of the cases are mild, although the pyrexia may be prolonged.

Here is a description of the average case as seen in the medical wards of a military hospital. The patient is admitted complaining of headache, with pains in the limbs and back, and there may be a slight cough. He feels ill, but does not look very toxic. The tongue is furred, constipation is usually present, the temperature is about 101°F and the pulse rate
is about 80 per minute. The temperature rises steadily in the first few days, and usually remains above the 101°F. degree mark, sometimes approaching 104 to 105°F. until it drops by lysis, in some cases, after ten days, but usually in from two to three weeks. The pulse-rate remains fairly steady, unless complications set in. Rigors are uncommon. The spleen becomes palpable on the third or fourth day, and this may be the only objective sign throughout the course of the disease. The headache usually disappears between the seventh and tenth day, and although the temperature remains high, the patient may look and feel well. The white count shows a slight leucopenia with a relative lymphocytosis, but this is not constant. The medical officer, who has had no experience of these cases, despairs of making a clinical diagnosis, but feels hopeful that the laboratory will come to his aid. Unfortunately the laboratory sometimes fails him in these cases.

Blood, feces, and urine are sent repeatedly for culture, with negative results. The last hope of making a positive diagnosis is by a rising Widal, but in a number of cases the result is disappointing.

Here are the Widal results of two cases: the first, typhoid fever, and the second, paratyphoid, in which the diagnosis was confirmed by positive blood and stool culture. In the first case *B. typhosus* was isolated from the blood on June 21, 1937, and the Widal results were:

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<tr>
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<th>24.6.37</th>
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<td>T.H.</td>
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In the second case *B. paratyphosus A.* was isolated from the blood on June 20, 1937, and the Widals in this case are a striking contrast to the first.

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<th>24.6.37</th>
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The following is the type of Widal from which the diagnosis is usually made. In this case *B. typhosus* was isolated from the blood.

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<td>T.H.</td>
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<td>B.H.</td>
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<td>T.O.</td>
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The case with a relative absence of specific agglutinins, quoted above, is not an isolated one, so one has to be prepared to make a diagnosis on clinical grounds alone, and ignore the findings from the laboratory. A clinical diagnosis of enteric group infection should never be made without repeated and thorough examinations of the case, and a careful consideration
of alternative diagnoses. The following points may help in differentiating this infection from other diseases which may closely resemble it.

Tropical Typhus is the first. I can only speak with experience of the type found in the Simla Hills, and this is very like an enteric group infection. Tropical typhus is a “place” disease, that is, it is endemic only in certain localities, and this is a useful point in the differential diagnosis. Clinically, a severe case of typhus looks more ill and prostrated than a severe case of enteric fever, and bronchopneumonia is commoner in the former disease. The suffused eyes and congested appearance of the face, which are characteristic of typhus, are only seen in the severe forms, while the typical rash occurs only in certain types of the disease. In the milder forms the diagnosis will have to be made by a positive Weil-Felix reaction, but when T.A.B. agglutinins rise in sympathy the picture becomes rather complicated, and the final diagnosis may be in the nature of a guess, rather than by scientific deduction.

Undulant or abortus fever, although not very common in India, has to be considered in the differential diagnosis. This disease is difficult to diagnose clinically in the early stage, but in the later stages it presents a fairly characteristic clinical picture, and resembles rheumatic fever rather than an enteric group infection. The patient does not usually look or feel ill, but the tongue is covered with a whitish fur, and obstinate constipation is the rule. The spleen is slightly palpable, and the pains in the joints and muscles, with the undulating type of temperature chart, lead one to suspect undulant fever, which is confirmed by the positive agglutination test. In every case of undiagnosed continued “fever” it is wise to have the serum tested for these agglutinins.

Amebic hepatitis, leading to hepatic abscess, is the next condition to be considered, and it is a very important one, as a wrong diagnosis may be fatal to the patient. It must first be strongly emphasized that an attack of amebic dysentery is not an essential preliminary to the above disease. In the cases I have seen, a previous history of dysentery has been the exception rather than the rule. Hepatitis and liver abscess are not complications of amebic dysentery, but are pathological conditions caused by the Entameba histolytica finding its way to the liver from the intestine. The mild case of amebic hepatitis is fairly easy to diagnose, and if there is any doubt about the etiology of the hepatitis, the therapeutic test—a course of injections of emetine—soon solves the problem. The patient complains of pain and discomfort under the right costal margin, and there is a low remittent fever. On examination, the liver is found to be palpable and tender, and in a mild case, this is usually the only sign of the disease. The stools should be searched for the vegetative or cystic forms of E. histolytica, but a negative result is of no consequence, and a course of emetine injections should always be given to these cases. The diagnosis of acute amebic hepatitis, with abscess formation, may be a much more difficult problem, and a mistake will be very serious for the patient. Acute
symptoms may appear suddenly in a previously healthy individual, and simulate those of typhoid fever very closely. The following case illustrates the difficulty in diagnosis, and also the importance of a thorough examination: The patient, a sergeant, was admitted to hospital complaining of a severe headache, backache, and abdominal discomfort. He had been quite fit up to the day of admission, and there was nothing relevant in his previous history. The temperature became high and continuous, a cough with muco-purulent sputum developed, and the patient looked very ill and toxic. The abdomen became distended and very tender, and there were signs of bronchopneumonia at the base of the right lung. His condition quickly became very serious, and the whole picture closely resembled a severe typhoid fever. The white blood count at that time was about 6,000 per cubic millimetre with a normal differential count.

It became very difficult to examine the abdomen owing to the severe pain, but careful palpation revealed that the distension was due to an enormously enlarged liver which was extremely tender. Later, a pleural effusion developed on the right side, and the blood showed a polymorphonuclear leucocytosis. A course of emetine injections was given, and the patient's condition slowly improved. An abscess was aspirated from the right lobe of the liver, the fluid in the pleura was drawn away, and the patient made an excellent recovery. A case like this points a moral: "If there is any doubt, give emetine." In these acute cases there are always signs at the base of the right lung, perhaps only a few crepitations, but more usually signs of bronchopneumonia or a pleural effusion. The patient has a peculiar sallow appearance which is characteristic of hepatic abscess.

Pain in the right shoulder is by no means a constant sign, and the white blood count, in the early stage, cannot be relied on. An X-ray examination of the liver and right diaphragm is of great assistance, but in some cases the patient's condition does not permit this.

Perinephritis and perinephric abscess are diseases which, in the early stages, may simulate an enteric group infection, and, in the later stages, if right-sided, a liver abscess.

This condition is fairly easily diagnosed if there has been a previous pyelitis pointing to an infection of the kidney, but in the blood-borne infections with no urinary signs, the cause of the fever may be very obscure. In the majority of cases the patient complains of pain in the renal area, which may, however, be very slight, and there is always tenderness in the affected region. The blood shows a polymorphonuclear leucocytosis, and in the later stages, when the hectic type of temperature and rapid pulse, with rigors and sweats, point to pus formation, the swelling in the renal area clears up the diagnosis.

But these cases are very worrying and not easy to diagnose, and perinephric abscess must always be considered in the investigation of a long-continued unexplained fever.

An early case of kala-azar presents a problem in diagnosis. Later on,
the enlarged spleen and liver, the positive Fermo-gel test and the marked leucopenia lead one to suspect the disease, and the diagnosis is established by finding Leishman-Donovan bodies in a smear from the spleen or liver.

Kala-azar is essentially a "place" disease—it is endemic in Assam, Bengal, and along the East Coast of India; it rarely penetrates further west than Lucknow. It must be remembered, of course, that the disease may remain latent for a long time, and symptoms may appear in a patient living in some other part of India who is really a native of, or has been stationed in, one of the endemic centres.

The temperature is remittent in type, and sometimes shows a double rise in the twenty-four hours. The patient does not usually look or feel ill, his tongue is clean, and his appetite is not affected. The spleen is only slightly enlarged in the early stages, and the blood shows a leucopenia with a relative lymphocytosis. Unfortunately, the Formo-gel test is not positive during the first three months of the disease, so a diagnosis can only be made by finding the parasites in the smear from either a splenic or liver puncture. In some cases, particularly in those from Madras, the Leishman-Donovan bodies are found in the peripheral blood. Medullary puncture of the tibia by a special trocar may be done, when the Leishman-Donovan bodies may be demonstrated in a smear from the red bone marrow.

In the differential diagnosis of any continued fever, tuberculosis, in its various forms, always plays an important part. In fact, it is often diagnosed too readily. The common pulmonary variety is not easily missed, but the "typhoid" form of acute miliary tuberculosis presents a much more difficult problem and, as its name implies, is apt to be confused with typhoid fever.

In acute miliary tuberculosis the temperature is more intermittent in type, and in some cases the rise occurs in the morning instead of the evening. The pulse is more rapid and cyanosis, with dyspnoea, is more marked. Eventually, focal signs appear, either in the lungs or brain, which make the diagnosis clear.

Early tuberculous disease of bone may be responsible for a long-continued pyrexia, with no obvious physical signs to account for it. In one case, after a continued fever of over six weeks, the patient complained of pain in the left buttock, and an X-ray revealed early tuberculous disease of the left hip-joint. Probably a careful clinical examination might have discovered this earlier, but in the absence of leading symptoms these cases can be very difficult.

Tuberculous disease of internal lymph glands in the abdomen and chest is sometimes responsible for an obscure pyrexia, but eventually the symptoms and signs lead to a radiological examination of these regions, and the cause is discovered.

A small pleural effusion, as the cause of a low remittent form of continued fever, may escape detection if the chest is not carefully examined from day to day. The rarer forms, encysted interlobar and diaphragmatic effusion, cause more difficulty, and a diagnosis may only be made with certainty after a radiological examination of the chest.
It must not be forgotten that an *empyema*, especially the streptococcal variety, may develop insidiously, and may be overlooked if the chest is not repeatedly examined.

Bronchopneumonia and abscess of the lung should not cause much difficulty as the clinical picture of both diseases is fairly obvious.

There are certain forms of septicæmia which cause prolonged pyrexia and in which physical signs may be indeterminate or absent.

Subacute bacterial endocarditis is an example, and in the early stages of the disease diagnosis may be very difficult. The two diseases which it resembles most are typhoid fever and miliary tuberculosis.

The temperature is of the irregular remittent type, the spleen is enlarged, and in contrast to the above two diseases, the blood shows a leucocytosis, not a leucopenia. Unfortunately, definite signs in the heart may not be evident at first, and blood culture in the early stages is usually sterile. Arterial emboli are important complications of this disease, and these should be searched for most diligently. They may appear in the form of small petechiae in the skin, a splenic infarct causing extreme pain, or emboli in the kidney, resulting in either a gross hæmaturia, or merely a few red cells in the urine.

Consequently, it is important to examine the urine daily for signs of these emboli. In the later stages of the disease the characteristic signs appear, and blood culture is usually positive.

Meningococcal septicæmia sometimes produces a pyrexia which may be prolonged over three to four weeks, and if meningeal signs are not prominent, or absent, the case is difficult to diagnose. These cases commonly occur during an epidemic of cerebrospinal meningitis, and on the slightest sign of neck rigidity, a lumbar puncture should be done and the fluid examined. The sporadic case may be very obscure. One case was diagnosed as undulant fever, owing to the severe pains in the muscles and joints.

Streptococcal and staphylococcal septicæmias, which appear "out of the blue," are very puzzling until the organisms are cultured from the blood. There is usually a marked polynuclear leucocytosis pointing to the presence of pus, and if no pus can be detected anywhere, septicæmia must be suspected. In these cases symptoms and physical signs change from day to day. There may be signs of pleurisy or pneumonia, which disappear quickly to give place to severe abdominal pain and diarrhœa. These rapid changes of signs and symptoms should rouse suspicions of a septicæmia.

There are many other causes of prolonged pyrexia, some very rare, but in most of them the diagnosis is fairly obvious.

Glandular fever, in its atypical form, in which there is no marked enlargement of lymphatic glands, and no throat signs, may cause difficulty, until the lymphocytosis, with the presence of abnormal cells, puts one on the right track.

The Pel-Ebstein type of fever, associated with Hodgkin's disease may be very obscure if the internal lymph glands are the only ones affected.
The leukemias are sometimes responsible for a low continued temperature, but examination of the blood at once points to the cause.

Dental and tonsillar abscesses are mentioned as causes of prolonged pyrexia, but this must be very uncommon.

Finally, there are the few cases which defeat diagnosis and are given that very unsatisfactory label—P. U. O. My opinion is that most of these cases are examples of one of the enteric group of diseases, or of tuberculous infection.

The diagnosis of a case of prolonged pyrexia is often a very fascinating study, comparable to the elucidation of one of these intricate problems of crime detection, and like the latter, the most trivial clue should not be neglected.

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