THE INVESTIGATION OF PROLONGED PYREXIA

By T. W. PRESTON, M.D.(LOND.), M.R.C.P.(LOND.)

*Physician, Croydon General Hospital; Hon. Lieut.-Col. R.A.M.C., lately Officer i/c of a Medical Division
India Command*

Preliminary Considerations

By prolonged pyrexia will be understood pyrexia of over ten days' duration. For the purposes of this article it will be assumed that a careful clinical examination has failed to reveal physical signs of a definite character.

Confronted with such a case it will rarely be possible to make an immediate diagnosis and investigation resolves itself into carrying out certain routine tests which will reduce a large number of "possibles" into a lesser number of "probables" from which the final diagnosis can finally be determined by some specific test. The late Sir Raymond Crawford was fond of saying to his students, "Rare things are rare and common things are common," and this is an adage which may profitably be borne in mind in this type of case.

At this stage, the following investigations should be carried out as routine.

(1) *Leucocyte and differential leucocyte count.*—A high polymorphonucleocytosis will make it extremely probable that the patient is suffering from some pyogenic infection—very probably a hidden collection of pus, and further investigations should be concentrated in this direction. A leucopenia, especially with a relative lymphocytosis, will indicate an entirely different field for further inquiry, whilst large numbers of monocytes or eosinophiles will definitely narrow the field. Where the picture is indefinite, repeated counts at three-day intervals should be made. It must be remembered that the picture may vary from day to day and, moreover, the picture may be misleading if the patient has been having a course of sulphonamide.

(2) *Blood culture.*—One sample of blood should be cultured on glucose broth, a second on a medium, suitable for the isolation of the Enteric Group (e.g. McConkey's medium). A positive culture will usually be conclusive but a negative result excludes nothing.

(3) *Agglutination reactions* against *B. typhosus* and *B. paratyphosis A. and B.*; *M. melitensis* and

Br. abortus of Bang. A single reading against the enteric group will frequently be inconclusive (especially if the patient has been inoculated), but a series of three tests at two-day intervals may show a rising titre of diagnostic significance.

(4) *A blood film* should be examined for malarial parasites if the patient has lived in a tropical or sub-tropical country; if necessary this should be repeated several times, if possible during a rigor.

Pending the result of these investigations, the case will be carefully reviewed, a study made of the type of fever as shown by a four-hourly chart and inquiry made into the patient's recent and remote movements. This is particularly important at the present time when so many men and women have recently returned from military service overseas. In considering residence overseas it is desirable to ascertain with some accuracy the particular location and in obscure cases to consult the relevant authorities as to the diseases endemic and epidemic. A general statement that the patient has been "in Africa" or "in India" may lead those unfamiliar with these countries to waste time looking for diseases which in fact never occur in the areas concerned.

An ex-soldier was suffering from an obscure pyrexia. Information that he had served in India led the doctor in charge to institute investigations for Kala-azar. More detailed inquiry showed that in India he had been stationed exclusively in Hyderabad state and Bombay Presidency—areas in which Kala-azar is as little prevalent as in the Isle of Wight.

After these preliminary considerations, the various diseases likely to be the cause of prolonged pyrexia may be enumerated and briefly reviewed. They may conveniently be subdivided into the following groups:

(a) Diseases of World-Wide Incidence.

- i. Likely to be associated with a polymorphonucleo-leucocytosis.
- ii. Likely to be associated with a leucopenia.
- iii. Likely to be associated with an indefinite blood picture.

(b) Diseases peculiar to certain areas.

(a) (i) Diseases of World-Wide Incidence Associated with Polymorphonuclear Leucocytosis.

i. *Septicaemia* (including Bacterial Endocarditis).ii. *Pyæmia*.

iii. *Hidden collection of pus*.—It is neither practicable nor desirable to discuss the numerous conditions included under this heading, but special mention may be made of perinephric abscess and "carbuncle of the kidney." There are probably few clinicians of experience who have not at some time had under their care cases of obscure pyrexia which have long eluded diagnosis and which have ultimately turned out to have had a perinephric abscess. In view of the obscure signs, special attention should always be concentrated on the exclusion of this most difficult condition. A previous history of boils will lead to a suspicion of the closely allied condition of "carbuncle of the kidney." (*En passant*, a warning may be uttered at the too facile dismissal of a staphylococcus grown from blood or urine culture as a contamination. Mention may be made of a case ultimately diagnosed as carbuncle of the kidney which had remained undiagnosed for many weeks. Perusal of the case papers revealed that early after admission a urine culture had grown a staphylococcus—and disregarded.)

(a) (ii) Diseases of World-Wide Incidence Associated with Leucopenia.

i. *Enteric Group of Fevers*.—It is essential to exclude this group in any case of prolonged pyrexia. Characteristically the temperature chart will show a step-like rise and a relatively slow pulse, but all types of fever may occur. Although commonest in tropical countries, especially when associated with faulty hygiene, it occurs sporadically and in minor epidemics in this country.

The surest method of diagnosis is by blood culture. This is most likely to be positive in the early stages but is well worth carrying out at any stage.

Failing a positive blood culture, isolation of the bacilli from the stools is successfully undertaken in many cases when an efficient technique is employed; although most likely to give positive results after the third week, an increasing number of bacteriologists are now successful in the early stages.

Agglutination Reactions:

"H" agglutination is indicative of infection with the homologous organism in an uninnoculated

person. If the patient has been previously inoculated however (even twenty years previously) H-agglutination is valueless.

"O" agglutination is not specific for separate members of the "E" group but is not produced by innoculation. Hence, a rising titre in serial tests is of diagnostic significance of enteric infection but is not specific.

"V" agglutinins are highly specific.

It is suggested that the terms "+ Widal" and "— Widal" should be abandoned as valueless and misleading; the only report of clinical value is a rising titre in at least two and preferably three tests done at two-day intervals.

2. *Undulant Fever (Abortus type)* is seen occasionally in all parts of the world. Clinically it is milder than *Melitensis* infections (see under (B)); it has few characteristic features of diagnostic significance and it is rarely diagnosed until it has run for many weeks and numerous investigations made with negative result; if the pyrexia assumes the characteristic undulant type the case may be suspected clinically; but frequently the fever is continuous or irregular. Diagnosis is established by agglutination of 1-100 or more to Br. *Abortus* of Bang. Infection is due to ingestion of infected milk or contiguity to infected animals, but often it is impossible to trace any connection and the clinical history may be most misleading.

A soldier was admitted to a Military Hospital in Scotland with the following history: Six weeks previously whilst stationed in the English Midlands he had been admitted to hospital with acute tonsillitis; contrary to established practice his tonsils had been enucleated during the stage of acute infection. After a stormy convalescence he was sent on leave to his home in Scotland where he spent most of the time in bed feeling unwell and running irregular fever. At the expiration of his leave he consulted a local doctor who sent him to the nearest Military Hospital as a "P.U.O." Physical examination was negative and although blood culture was sterile a provisional diagnosis of streptococcal septicaemia seemed, under the circumstances, not unreasonable. This diagnosis seemed strengthened when the temperature subsided coincidentally with the exhibition of sulphonamide. After a few days, however, the temperature rose again, and the diagnosis was only established several weeks later when agglutination to Br. *Abortus* was obtained in high dilution.

3. *Agranulocytosis*.—This condition is to be borne in mind especially in view of the prevalent, and sometimes injudicious, use of the sulphonamide group of drugs. Differential diagnosis may be difficult from aplastic anaemia, acute aleukaemic leukaemia and acute mononucleosis. Examination of sternal marrow by a skilled haematologist may help.

(A) (iii) Diseases of World-Wide Incidence with Indefinite Blood Picture.

i. *Atypical Pneumonia*.—Usually the fever sub-

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sides within 10 days, but in more prolonged cases the absence of physical signs will make diagnosis difficult. There may be an increase of monocytes. The diagnosis can only be established by radiography.

2. *Influenza*.—Except in epidemics, this diagnosis should never be made until other conditions have been excluded; the diagnosis should only be provisional so long as fever persists and investigations must be continued. There may be leucopenia and the pulse relatively slow, but these findings are inconstant. If fever persists for more than two weeks it is wise to assume either that the diagnosis is wrong or that there are complications (especially pneumonia or empyaema).

3. *Acute Miliary Tuberculosis*.

4. *Relapsing Fever*.—Although commonest in the East, it occurs in Europe and is reported from time to time in Ireland (louse-borne). (The tick-borne occurs in Central Africa.) It is characterised by five to seven days of high fever followed by a crisis and ten to fourteen days remission followed by relapse. This may be repeated once or several times. Diagnosis is established by detection of the spirochaete in thick blood films taken during fever.

5. *Rat-Bite Fever* produces a relapsing type of fever difficult to distinguish from relapsing fever. There may be a polymorphonucleocytosis. The history, local lymphangitis and a raised erythematous rash will direct the diagnosis. The causative spirillum may be found in the blood but its isolation is difficult.

6. *Typhus Fevers*.—The true louse-borne or epidemic typhus is world-wide. Tick-borne, mite-borne and flea-borne varieties occur endemically, various sub-types in various districts. In endemic areas and in epidemics diagnosis on clinical grounds is easy, otherwise diagnosis is established by the Weil-Felix reaction. (Note: sporadic cases are unlikely.)

7. *Glandular Fever*.—The common glandular types and the rare Anginose type do not call for description in a discussion on Prolonged Pyrexia. The febrile type, however, may present extreme difficulties in diagnosis. Adenitis may be transitory and too slight to be significant, and clinically the course and symptoms may be uncharacteristic. Pyrexia may be prolonged with recurrences and apyrexial periods. Undulant fevers, lymphadenoma and leukaemia may be suspected. Although monocleosis is characteristic (and probably always occurs at some stage), the blood picture is extremely variable and may change from day to day. There may be leucopenia or leucocytosis and polymorphs, lymphocytes or monocytes may predominate. In suspected cases repeated blood examinations should be made. A count of over

30,000 per c.mm. is unusual and raises suspicion of a leukaemia. A positive Paul-Bunnell reaction in a titre of 1-64 is diagnostic. (There is no doubt that this group calls for further clarification.)

8. *Lymphadenoma* may be associated with pyrexia of a relapsing type (Pel-Ebstein) or irregular. The blood picture is not characteristic and diagnosis can only be established by biopsy of a gland. Great difficulty in diagnosis may occur when the mediastinal or mesenteric glands are enlarged with no appreciable superficial adenitis.

9. *Leukaemias*.—Atypical leukaemias with pyrexia and aleukaemia may present difficulty. Diagnosis depends on repeated blood examinations and examination of sternal marrow by a skilled haematologist.

(B) Diseases Peculiar to Certain Areas.

1. *Malaria*. With a history of relapse in a tropical or sub-tropical country it is always necessary to exclude malaria. The following practical points should be borne in mind:

Duration of liability to relapse: M.T., rare after eighteen months; B.T., common up to two years and may be up to three or four years; Quartan, very persistent—four years or more.

Well-authenticated cases have occurred apparent first attacks in this country in persons who have not had clinical malaria overseas.

One negative blood film does not exclude malaria; it may be necessary to examine many films before parasites are found—preferably taken during a rigor.

A soldier was admitted to hospital in India with persistent pyrexia. Six blood films were taken and examined by an experienced pathologist with negative results. A seventh film was literally swarming with M.T. parasites.

Occasionally parasites (especially M.T.) may be discovered on sternal puncture which have eluded detection in blood films.

It is emphasised that the characteristic regular intermittent fever may be replaced by a fever irregular or continuous.

Occasionally it is justifiable to try the therapeutic effect of Quinine in spite of negative films.

2. *Kala-azar (Leishmaniasis)*.—Although fairly wide-spread this condition has a somewhat patchy distribution and is practically unknown in some areas in close proximity to others where it is common. In Africa it is mainly found on the East coast, in Sudan and the Blue Nile, Ethiopia, and on the Mediterranean coast; in Europe, on the south coast of Spain, Malta and Crete, Sicily and the "toe" of Italy. In India—a few cases occur in Madras—then passing north the country

is free of it until we come to the Ganges delta; it is common in Bengal and Assam, but is never met west of Lucknow, Western India being free. It occurs in parts of China, Manchukuo, Mongolia, Transcaucasia, and Russian Turkestan, and in parts of South America.

The fever is characteristically remittent, dropping in the morning, rising in the early afternoon, falling again towards evening, and rising again during the night. This will be shown by keeping a three-hourly chart. This may continue for many weeks followed by a period of partial apyrexia followed by a relapse. This may continue for many months.

Absence of malaise and symptoms may be striking. It is a clinical experience never to be forgotten to visit a hospital where cases of Kala-azar are being treated; to inspect first the temperature charts showing fever to 103° and 104° , and then to see the patients sitting up in bed eating a hearty meal and demanding to be allowed up! It is frequently difficult to persuade Indian and African patients to remain in hospital and often impossible to confine them to bed.

Leucopenia is a striking and constant feature—usually below 3,000 per c.mm. and often down to 1,000 per c.mm., the deficiency being mainly in polymorphs.

Enlargement of the spleen occurs approximately at the same rate as the pregnant uterus in the opposite direction. Thus in early cases the spleen will be just palpable, in a case of six months duration it may be expected in the region of the umbilicus.

Diagnosis can only be established by demonstrating L-D bodies in material obtained by sternal or splenic puncture. Although less reliable, sternal puncture should always be tried first on account of its greater safety and the material cultured as well as examined in direct films. Splenic puncture should be performed by a rapid thrust with a fine-bore needle; the drop of fluid thus obtained is quite sufficient for examination. Prolonged aspiration through a wide-bore needle is unnecessary and dangerous. It is emphasised that recognition of L-D bodies requires the familiarity which is only gained by experience. It is futile for the clinician to subject his patient to the inconvenience (and possible danger) of sternal or splenic puncture unless he has arranged

for the material to be examined by a pathologist experienced in Kala-azar.

Napier's Aldchyde test is valuable and easily carried out, but it rarely gives a positive result until the disease is of three to four months duration. It is therefore useless for early diagnosis, but a negative reaction in a case of long-standing illness can be safely taken to exclude Kala-azar. Doubtful positive reactions are stated to occur in certain other diseases (advanced tuberculosis, and leprosy).

3. *Undulant Fever (Melitensis type)* is widespread in goat-rearing districts of the tropics and sub-tropics. The undulant character of the fever is more constant than in the Abortus type and usually the patient is more ill. Sweating may be profuse and there is complaint of headache, a picture which may be mistaken for acute rheumatism. The spleen may be enlarged. The pulse is relatively slow. There is usually leucopenia with relative lymphocytosis. Agglutination to 1-100 or over to *M. Melitensis* establishes the diagnosis.

A soldier was invalided home from North Africa as a case of Pulmonary Tuberculosis. His prolonged fever seemed inconsistent with the apparently healed and inactive tuberculous focus seen radiologically. Agglutination reactions gave a strong positive to *M. Melitensis*.

4. *Amoebiasis*.—It may appear that reference to this condition is out of place in a paper on prolonged pyrexia since localising symptoms and signs might reasonably be anticipated. It is emphasised, therefore, that Amoebic Dysentery is occasionally an insidious disease and sometimes symptoms may occur ten years or longer after original infection (which may never have been diagnosed). When, therefore, obscure pyrexia occurs in persons with a past record of tropical residence, examination of the stools and careful palpation of the liver is indicated. Sometimes a liver abscess may occur in an impalpable liver and only recognised by "humping" of the diaphragm revealed by screening. (Note: such a liver, however, would usually be painful on pressure over the intercostal spaces.) It may be noted that whilst a leucocytosis (with increased polymorphs) is usual it may be only of moderate degree and may be absent. In Endemic areas the therapeutic effect of emetine is sometimes regarded as a useful and justifiable test.

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