Current Practice

CHILD CARE IN GENERAL PRACTICE

Undiagnosed Fever

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In any consideration of undiagnosed fever it is necessary to ascertain, if possible, whether there is an accepted meaning of the term. There is certainly no official definition and the time that a temperature remains undiagnosed before it is regarded as of unknown aetiology, and the criteria adopted by various authors, differ widely. Even for adults there does not appear to be any uniformity of opinion and for children hardly any opinion at all.

Problems of Definition

Reid (1956) suggested that pyrexia of unknown origin (P.U.O.) existed in a patient over 14 years who presented with fever as the dominant sign, was considered after initial examination and radiograph of the chest to have insufficient localizing symptoms and signs to be diagnosed with confidence, and whom it was proposed to investigate in the manner customary for such cases. A temperature of 100.4° F. (38° C.) on one occasion or 99.4° F. (37.4° C.) on three occasions was thought to meet the required degree of pyrexia. Petersdorf and Beeson (1961), on the other hand, considered that the illness must have lasted three weeks or more, the temperature must have been higher than 101° F. (38.3° C.) several times, and the diagnosis must still be uncertain after a week of hospital investigation. Some point between these two extremes of opinion seems to be reasonable, and I would regard a temperature of 101° F. (38.3° C.) or more, running for five to seven consecutive days without localizing signs, necessary before embarking on the routine investigations, though serious illness would indicate urgent attention.

In general practice the definition of P.U.O. is much less precise. When patients are admitted to hospital by the family doctor the label often means that the patient has continued to have a temperature, not necessarily high, for some days without adequate cause being found after examination and such investigations as are possible at home. In addition, the temperature has usually persisted in spite of the administration of sulphonamides, oral penicillin, and often broad-spectrum antibiotics, though not always in effective dosage or for adequate time. The usual stage at which hospital admission is requested is between four and seven days from the onset and depends on how soon the family doctor senses that the relatives are becoming anxious and restive.

Incidence

The incidence of such cases is not easy to determine, because even in hospital cases the admission diagnosis may be "query enteric" or "query chest infection" rather than P.U.O., which the practitioner often feels implies a failure of diagnosis, unless he is on friendly terms with the hospital staff. In my unit,

which deals particularly with acute febrile illness, the incidence is over 3%.

During the period 1957 to 1963 165 cases were admitted with a diagnosis of P.U.O. The discharge diagnoses of these cases were as follows:

Upper respiratory infection (nasopharyngitis, tonsillitis, otitis media)	30
Lower respiratory infection (bronchitis, pneumonia)	24
Urinary infection (pyelonephritis)	10
Alimentary infection (typhoid, 3; appendicitis, 3; mesenteric adenitis, 2)	8
Sepsis (abscess, cellulitis, osteitis)	7
Mononucleosis	5
Abortus infection	2
Tuberculosis	5
Collagen vascular disease	9
Neoplasm	3
P.U.O.	9
Unrelated conditions	18
No abnormality found	35

A comparison with adult cases over the same period shows that undiagnosed fever is common to both groups and remains undiagnosed in nearly the same proportions in each. Infections of the respiratory tract are common to both and are often caused by viruses or inadequately treated pyogenic infections. Most of these conditions are of shorter duration and clear quickly after admission to hospital. Mononucleosis, influenza, and tuberculosis are more often encountered in adults, while urinary infections, rheumatic and alimentary conditions, and sepsis are seen more frequently in children.

The majority of those cases which satisfy the criteria of undiagnosed fever and usually require investigation are eventually found to be unusual manifestations of common diseases rather than rare or exotic conditions, though the latter do occur and may be among the most difficult to elucidate. The three groups of conditions most commonly encountered are infection, collagen vascular disorder, and neoplasm.

Infection

Viruses

Viruses are rarely the cause of prolonged pyrexia but commonly of fevers with an acute onset and of medium duration. It should be remembered that one child in five may be febrile throughout the incubation period of measles, which may be associated with delirium and convulsions. These signs appear to be without cause, unless definite contact with a case of measles is known or until the catarrhal phase begins. Similarly, in hepatitis the illness may be non-icteric and pyrexial, though profound anorexia, nausea, and vomiting should suggest the diagnosis, which may be confirmed by examination of the blood, urine, and faeces, or rarely at necropsy after sudden and unexpected liver necrosis. In the neonatal period similar illnesses can result from infection by the viruses of herpes simplex and varicella and the protozoon of toxoplasmosis. Mononucleosis is often difficult to diagnose in young

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children, the characteristic glandular swellings, splenomegaly, or throat involvement not being apparent for many days or never occurring, and the typical blood picture and Paul-Bunnell reaction long delayed or totally absent. Acute myocarditis, presumably of viral origin though often unproved, can be very baffling and is initially considered to be rheumatic. It may persist for some weeks even in non-fatal cases. The following case illustrates acute myocarditis of unspecified origin.

Case 1.—B. W., aged 2 years, was admitted after 10 days of pyrexia with signs of heart failure. Radiographs confirmed clear lung fields but revealed a large heart, and an E.C.G. showed changes of acute myocarditis. Treatment improved the failure, but the temperature remained intermittent and a further episode of acute failure occurred. Abnormal heart sounds, E.C.G. changes, and liver enlargement persisted for 18 months. Ultimate recovery was complete. There was no laboratory evidence of rheumatic or viral infection.

Pyogenic Infection

Pyogenic infection of the kidney and renal tract is relatively frequent and it must be remembered that this may not necessarily be the primary cause of the pyrexia under investigation. In children fever may be intermittent for many days without symptoms pointing to the urinary tract appearing, and sometimes such symptoms may never be present. Pyuria also is very intermittent, and repeated specimens of urine may be normal before a phase of pyuria, lasting only hours, occurs. Abnormalities of the urinary tract are not infrequently found in such cases and an abnormal pyelogram in a 6-week-old baby led to laparotomy, when biopsy of the kidney revealed pyelonephritis. Perinephritic abscess may be suspected by vague local tenderness without definite signs, and may subside on antibiotic treatment before a certain diagnosis can be achieved.

Staphylococcal and streptococcal infection of bones, particularly of the pelvis, scapula, and even the spine, may remain undiagnosed for a considerable time before obvious localizing signs attract attention. Retroperitoneal and subphrenic abscess are also singularly silent in the initial stages, even when occurring after lesions of the appendix. The association between steroids and pyogenic infection must never be forgotten in cases of obscure fever.

It is perhaps worth noting that subacute bacterial endocarditis rarely occurs in children nowadays as a cause of P.U.O. This is no doubt because children suffering from rheumatic and congenital heart disease are more carefully supervised and have long-term chemoprophylactic treatment and additional antibiotic cover for all acute infections and such minor surgical procedures as dental extractions.

Salmonella Infection

When salmonella infection is due to *Salmonella typhi* or *paratyphi* it is usually diagnosed quickly because these organisms are well known as causes of undiagnosed fever. It is not perhaps appreciated that salmonella of the food-poisoning type may also cause septicaemia resembling typhoid and occasionally a more chronic infection with prolonged temperature and lymphadenopathy, as was seen in the following case.

Case 2.—G. D., aged 5 years, had a long history of fleeting swellings affecting face and limbs, later thought to be due to the Henoch-Schönlein syndrome. Loose stools, loss of weight, and lumps in the neck brought him to hospital, where pyrexia, ascites, lymphadenopathy, hepatomegaly, anaemia, and infiltration of the lung suggested reticulosis. This was not confirmed by gland biopsy. Faeces culture revealed *S. dublin*, which was thought to be coincidental and which responded to antibiotic treatment. Pyrexia recurred, and a further gland biopsy showed the presence of Gram-negative organisms, confirmed by fluid aspirated from other glands and antibody titres of 1/80,000. Prolonged treatment over many months effected a complete cure.

Brucellosis

Brucellosis is particularly difficult to diagnose in children, perhaps because the tissue reaction at this time of life is not very brisk to abortus infection and pyrexia is of a lower grade, especially if the condition has passed the initial acute phase. The symptoms are non-specific and consist in a variety of vague complaints, common among which are fleeting bone, joint, and muscle pains, sweating, listlessness, and disinclination for activity, though the general physical condition is well preserved. Unless brucellosis is kept in mind a diagnosis of hysteria or neurosis is easily made. Blood culture is seldom positive except in the very early stage and agglutinations may be initially of a low titre; repeated testing, days or weeks after a brucellin skin test, may be required to show a rising titre. Blocking antibodies and a positive Coombs test are of additional value, but liver biopsy is said to be confirmatory—though perhaps unjustified in this condition.

Tuberculosis

Tuberculosis is no longer a frequent cause of illness in children, only one-tenth of the notified new cases belonging to this age group, and so it may be overlooked. This situation is no doubt due to B.C.G. inoculation and careful tracing of contacts. It is thus evident that tuberculosis is an even less frequent cause of undiagnosed fever, though rarely miliary or disseminated disease may be encountered. In difficult cases the Mantoux reaction may be repeatedly negative up to concentrations of 1 in 10. The symptoms often suggest arthralgia or rheumatism, lymphadenopathy, or leukaemia. The E.S.R. is usually though not inevitably high, sputum and C.S.F. examinations often negative, and radiograph of the lungs either normal or showing fine and indefinite reticulation. The diagnosis may be ascertained at necropsy. Concurrent steroid therapy should always alert suspicion. Examination of the family contacts may reveal a possible infecter or other childhood cases.

Collagen Vascular Diseases

This is a not infrequent cause of undiagnosed fever, the milder and subacute forms of rheumatic fever and the early stages of Still's disease being the usual manifestations. Symptoms are vague, and generalized aching without either polyarthritides or the other common stigmata of rheumatic fever—especially when the heart is not affected—gives little indication of the cause of the pyrexia. Fleeting rashes of the erythema marginatum type may provide a clue, but a high E.S.R. and white-cell count, a high A.S.O. titre, and C-reactive protein, are strong supporting evidence of rheumatism. This is occasionally true of Still's disease, which may be solely pyrexial for a long time before typical rheumatoid involvement of joints becomes manifest. In the early phases lymphadenopathy and slight splenomegaly associated with rashes of variable and fleeting appearance may suggest the diagnosis, and this suspicion may be heightened by an elevated white-cell count and E.S.R. and a change in plasma proteins with a rise in gamma-globulin. The Rose-Waaler and latex-fixation tests are seldom helpful and it is not until typical rheumatoid joint manifestations appear that the true diagnosis can be made. The following case illustrates this.

Case 3.—S. B., aged 12 years, was feverish with pains in knees and elbows and one hip for one week. She vomited and was anorexic, had a vague sore throat and then intermittent pains, and was anxious and ill. Her temperature was 103° F. (39.4° C.), her skin moist, and she had lost much weight. There was tenderness over the left wrist and knee and her hands were sore, but no objective signs were present. The results of tests were: E.S.R. 62, A.S.O. titre 30, latex-fixation test negative, C-reactive protein +, Hb 11.5 g./100 ml., W.B.C. 19,000. There was no response to antibiotics. Blood-

stained vomiting occurred, and the haemoglobin level dropped to 9.9 g./100 ml. A laparotomy was done to exclude neoplasm. The high temperatures continued for a month, when typical rheumatoid swellings of a wrist and ankle developed. Response to steroids was eventually complete.

Other allied diseases such as periarteritis nodosa (without hypertension, albuminuria, and eosinophilia initially), disseminated lupus erythematosus (often without L.E. cells in the blood), dermatomyositis, and sarcoidosis are rarely seen in childhood but account for some of the most baffling examples of P.U.O.

Neoplasm

In childhood, neoplasm may sometimes give rise to prolonged pyrexia before any localizing signs appear. In the early years of life reticulosis of the Letterer-Siwe type, neuroblastoma, and acute leukaemia are encountered, while in later years Hodgkin's disease and reticulosarcoma are more likely to occur. Night sweats are frequent in both these conditions, but the typical Pel-Ebstein temperature is seldom seen. In many cases diagnosis is not made without laparotomy or at necropsy, and this is especially so in the rarer neoplasms of the thoracic and abdominal viscera.

The following is a case of acute reticulosis.

Case 4.—B.H., aged 4 years, developed toothache and pain in the neck and had fever and enlarged cervical glands for 10 days. His temperature was persistently 103° F. (39.4° C.) throughout. The child was miserable, with generalized lymphadenopathy and splenomegaly. The results of tests were: W.B.C. normal, Hb 7 g./100 ml., agglutinations and radiographs of the skeleton were normal. There was slight glandular enlargement and ascites, and hepatomegaly. Reticulosis was confirmed at necropsy three weeks after admission.

What Should the Doctor Do?

How then should the family doctor act when confronted with a case of suspected undiagnosed fever? Initially he should make absolutely certain that there is in fact a sustained temperature. The taking of temperatures by parents without confirmation by the doctor is not always reliable and any slight deviations from the 98.4° F. (36.9° C.) range are regarded as constituting a "temperature" by many parents. The next essential is a thorough clinical examination, including urine microscopy on more than one occasion. Sometimes children are sent to hospital with a history of prolonged pyrexia and found to be afebrile after admission, or with some manifestations of upper respiratory infection or lung involvement accounting for the illness. If antibiotics are given—and in practice it is very difficult to resist pressure by the parents—they should be administered in adequate dosage, and by injection if appropriate, allowing reasonable time for the treatment to take effect. The subsequent course of action will depend on the severity of the illness, which may be of such a degree as to warrant early admission to hospital. Another factor is the extent of diagnostic facilities available to the doctor and his ability to use them, which may be limited by the length of time he can devote to such a problem in a busy practice at certain times of the year.

Routine Tests

When laboratory and radiographic facilities are easily accessible it should be possible to have the following routine tests carried out.

Blood Examination.—A total white-cell count and differential count may help to indicate pyogenic infection when a high polymorph response is found. Low counts are usually encountered in infections due to viruses, typhoid, tuberculosis, and occasionally with neoplasm. Mononucleosis and leukaemia can often be diagnosed on the first blood examination, though

in mononucleosis the initial count may be low and atypical until lymphadenopathy appears, while in leukaemia the peripheral blood may be normal for some considerable time, though the platelets may be low. A low haemoglobin may indicate malignancy and a high E.S.R. tuberculosis or collagen disease. Liver-function tests may be abnormal in hepatitis before jaundice appears.

Mantoux Testing.—This should be carried out routinely with a strength of 1/1,000 and up to a dilution of 1/10 if any doubt exists as to the possibility of contact infection.

Urine Examination.—Examinations, particularly in girls, should be repeatedly done on many days, and, even where no pyuria exists, clean mid-stream specimens obtained for colony counts. An abscess in the kidney may discharge intermittently and for a short time only and the pyuria is thus easily missed.

Radiographs of the Lungs.—These can exclude pneumonia or tuberculous infiltration, or may show an infected cyst or interlobar empyema not detected clinically.

Agglutination Reactions.—These reactions for enteric, salmonella, and abortus infections and a Paul-Bunnell reaction can also be obtained, though a negative result does not necessarily rule out infection, because antibodies are slow to develop.

Faeces Examinations.—Examining the faeces for occult blood and for bacteria is often indicated. Virus isolation may be carried out, but results are likely to be only of retrospective value, though perhaps important in an epidemic situation.

Admission to Hospital

When after these investigations no diagnosis can be made admission to hospital is certainly indicated. Here some of the foregoing tests may be repeated, especially agglutinations and blood culture, which should be done on several occasions at the height of the temperature, particularly if rigors occur.

Brucella skin-testing may provide confirmatory evidence, the test being read at least a week later and agglutinations sought again after this provocative stimulus. Plasma electrophoresis, marrow puncture, and the searching for lupus-erythematosus cells and antinuclear factor may be necessary, while intravenous pyelogram and radiographs of the skeleton may reveal primary or secondary neoplasm.

Biopsy of skin glands when these are palpably enlarged may be rewarding, part of the gland being sent under sterile conditions to the bacteriologist. Liver biopsy in children is not carried out by the percutaneous route in my unit, as it is felt that if this measure is necessary—and in such cases it must not be shirked—laparotomy is preferable because it allows an inspection of the viscera as well. Biopsy and laparotomy are not always helpful and are often disappointingly negative, but even negative information is sometimes valuable.

The majority of cases of prolonged pyrexia in children are eventually diagnosed. It must always be remembered that some children have an exaggerated response to minor infections and even to such conditions as anaemia, while in others a pyrexial state may be a sensitivity response to drugs and antibiotics administered in the treatment of an initial infection. Periodic pyrexia, as described by Reimann (1962), may be a definite entity, but a persistently normal temperature is just as rare. The tyranny of the thermometer should be avoided by parents and doctors alike.

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