Pyrexia of unknown origin sixty years on

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Introduction

Fever used to be regarded as a disease. This all changed when Gabriel Daniel Fahrenheit developed an effective thermometer at the beginning of the eighteenth century, and after Professor Carl Wunderlich of Leipzig introduced the concept of the temperature chart, using a thermometer a foot long and requiring twenty minutes to register the temperature. It soon became obvious that fever was not a disease in itself but merely a symptom. It is likely that Ludwig Traube (1818–1876) was the first physician to make a continuous temperature chart. Later, in 1867, Sir Thomas Clifford Allbutt (1836–1925), the Regius Professor of Physic at Cambridge, introduced the short, portable and rapidly readable thermometer and the investigation of fever and fever patterns commenced. As medical science progressed numerous causes of fever were discovered but there were always fevers whose cause remained problematical, and from time to time learned physicians discoursed and speculated on certain aspects of puzzling fevers.

One of these physicians was Sir Thomas Horder. Sixty years have passed since he published his reflective paper 'Some Cases of Pyrexia without Physical Signs' in the *Postgraduate Medical Journal* (Horder, 1925), and since then the practice of medicine has undergone major changes. Diagnostic techniques and therapeutic possibilities have proliferated. The health of the population has improved dramatically, and the pattern of diseases has changed dramatically. The population has also changed, as have patterns of their behaviour. All these factors have contributed to changes in the patterns of pyrexia of unknown origin (PUO).

Despite these changes I suspect the doctor's approach to patients with PUO is in essence very similar to that of Horder as some of his 1925 introductory comments still apply today. It is still true that 'there are plenty of acute febrile diseases in which it is quite impossible to say what is the nature of the illness unless and until certain symptoms and signs have developed.' It is still true that the evaluation of febrile patients is difficult because we initially 'never know whether the condition underlying an obscure

pyrexia is going to turn out to be trivial, or very serious.' It is still true that physicians, when asked by anxious relatives and friends 'what, exactly, is it doctor?' take refuge in 'a position where we have had to manufacture names which do not carry conviction to ourselves in order not to risk losing the confidence of those who put the question to us.'

There are differences however. Sixty years ago one could agonize over the possible diagnoses of a PUO, but because of a relative lack of powerful drugs, one could often enlist the help of time as a diagnostic aid. This diagnostic option is denied us today, and many of the more serious infection related diseases have now to be treated upon suspicion whilst awaiting results that confirm or deny our original suspicions. In 1953 Horder remarked that 'it was a common reflection a couple of decades ago that treatment lagged behind diagnosis.' Now, especially with seriously ill patients, diagnosis has to lag behind treatment. Apart from the presence of therapies unknown to Horder, patients today (or, to be more particular, their legal advisors) will not accept Horder's temporizing option concerning his patients 'My own feeling about many of them is, that they will be no worse if they become more definitely ill in order that they may be treated on some proper basis in regard to the diagnosis.' Current medical wisdom would not contemplate a 'pyrexia as an expression of an unstable nervous system' secondary to neurosis but there is no doubt that one sometimes wishes, as did Horder, that certain neurotic patients would 'stop taking the temperature and start on a system of gradual and encouraging re-education.'

Changing patterns of PUO

Horder obviously knew that fever could have many causes, both infective and non-infective, but he probably adhered to the classical teaching that the pattern of fever may be suggestive of certain diseases whereas contemporary opinions contend that the pattern of fever is hardly ever diagnostic (who can differentiate between the undulant fever of brucellosis and the Pel-Ebstein fever of Hodgkin's disease – some would dispute the existence of Pel-Ebstein fever, never mind

its significance) and on occasion the pattern of fever, like the much publicized relative bradycardia of enteric fever, may be positively misleading.

In their classical paper Petersdorf & Beeson (1961) gave criteria of PUO to be an illness of at least three weeks' duration, with fever (temperature exceeding 38.3°C on several occasions) and no established diagnosis after one week of hospital investigation. Such a definition excludes many transitory febrile illnesses which may well provide puzzling problems, especially as patients are commonly referred to hospital by modern general practitioners after only a few days of fever, and this speed of referral means that most PUO should be diagnosed before three weeks of fever have elapsed. The following review will not confine itself to fever of over three weeks duration.

Recent changes in the patterns of PUO can best be realized by comparing the findings of two similar papers, both having Petersdorf as one of the authors (Petersdorf & Beeson, 1961; Larson *et al.*, 1982).

The striking change is the greater proportion of neoplastic conditions. There are several possible causes for this change – alterations of referral patterns, and new techniques diminish the proportion of non-neoplastic disorders because they can be rapidly diagnosed and excluded from recent series. Just as interesting is the static proportion of patients with infection as a cause, and this despite major reduction in the incidence of many of the classical fevers, especially tuberculosis. Perhaps the reduction in classical pulmonary tuberculosis has led to a low index of diagnostic suspicion, especially in patients whose tuberculosis is extrapulmonary. This is unfortunate as tuberculosis is treatable. In the 1982 paper there were four patients with cytomegalovirus infection – a diagnosis which could not have been made in the first series of patients. Four patients had Still's disease in the second series and only two in the first. Clinicians should be more aware of this disease which is not restricted to young children, and as it may present with a PUO without arthritic clues to assist the diagnosis.

Table 1 Diagnoses on patients with PUO (Petersdorf & Beeson, 1961; Larson *et al.*, 1982)

	1961 Series	1982 Series
Infections	36	32
Neoplasma	19	33
Collagen/autoimmune	15	9
Granulomatous diseases	4	8
Miscellaneous	11	7
Periodic fever	5	0
Factitious fever	3	3
Undiagnosed	7	13
Total	100	105

tician (Bujak *et al.*, 1973). The decline in rheumatic fever (six patients in the 1961, one in the 1982 series) reflects the decline in serious streptococcal infections and their immunological sequelae. The reasons for this decline are still uncertain.

Surprisingly there were more undiagnosed patients in the second series (13 as opposed to 7). However, as all the undiagnosed patients in the second series were well at least one year after presentation it seems that medical science can now diagnose most serious illnesses that present as a PUO.

A notable absentee from both series is syphilis: which in one series in the past accounted for 11 out of 90 cases of PUO (Hamman & Wainwright, 1936); now few patients with puzzling illnesses escape serology.

The encyclopaedic classification of diseases that may cause a PUO is rather tedious but a diagrammatic approach is perhaps less tedious than most: Figure 1 details sites where the aetiology of PUO may remain hidden from clinical assessment. Horder was able to avoid the need for such encyclopaedic classifications by entitling his paper 'Some Cases . . .' It seems appropriate to mention here that the style of medical discourse has also changed markedly since Horder's days: what was personal and anecdotal has been replaced by the impersonal and rigorously scientific.

I will not dwell on the appropriate investigations for each disease process mentioned – suitable schemes have been published elsewhere (Daggart, 1976), but will mention particular aspects of certain illnesses which have altered over the last 60 years.

Gastrointestinal diseases

Occult neoplasia as a cause of PUO would have been known to Horder, as would ileocaecal tuberculosis, usually of bovine origin. He would probably have been aware of febrile patients whose illness was not characteristic of tuberculosis yet nevertheless had granulomata in the intestine at autopsy. It was not until 1932 that Crohn and colleagues have an account of a non-specific granulomatous inflammation distinguishable from tuberculosis, but Crohn's disease is now a well recognized cause of PUO.

Endocarditis

Rheumatic fever and its associated heart valve damage which predisposed to endocarditis was very common in the past but it is now almost extinct in Great Britain (Sutton & Rubenstein, 1974). In association with this the bacteriology and associations of endocarditis have changed (Hughes & Gauld, 1960; Welsby, 1977). Cardiac surgery, intravenous drug abuse, the decline in rheumatic fever, and probably the widespread use of

Figure 1 Sites where the aetiology of persistent pyrexias may remain hidden (from '*Infectious Diseases*', P. Welsby by kind permission of MTP Press.

antibiotics all have had a part to play. The confirmation of endocarditis is now far easier than in 1925; blood cultures are now routinely performed in most febrile hospital patients (blood cultures were in fact generally available before the early 1930s) and echocardiography is available after its development in the 1950s.

Liver abscess

Diagnosis and treatment is easier today than in 1925: Horder was well aware of the possible occult nature of liver abscesses and of their possible amoebic aetiology.

Giant cell arteritis

This is a notable cause of PUO, having an annual

incidence of about 3 per 100,000 population. Giant cell arteritis (GCA) includes temporal arteritis, the polymyalgia rheumatica syndrome, a combination of muscular and temporal symptoms, and 'general' symptoms, particularly PUO (Malmvall *et al.*, 1980).

Horder may well have been aware of a syndrome associated with giant cells as seen on microscopy of biopsy specimens, but he would not have had corticosteroids in his therapeutic repertoire and thus almost certainly he would have been familiar with the complications, including sudden blindness.

As a cause of PUO the polymyalgia rheumatica syndrome deserves particular mention. The presentation is usually with bilateral pain and stiffness in the proximal muscles, fever, fatigue, anorexia, and an elevated erythrocyte sedimentation rate in patients over 50 years of age.

There is a variant of GCA in which there are general symptoms only, and in some cases PUO can persist

until a temporal artery biopsy reveals GCA. However, a normal biopsy does not rule out GCA and many astute physicians learn when to desist from performing tests and to prescribe corticosteroids on the basis of the clinical picture and negative tests for other less likely pathologies. I well remember presenting a perplexing PUO at a clinical meeting and all my contemporaries vied with each other to suggest tests that I had not performed. The discussion ended when my erstwhile boss stood up and remarked 'Enough is enough. The patient's name is Smith. He therefore has Smith's syndrome. He will get better on steroids.' He did!

Kidney

Hypernephroma and urinary tract infection may produce fever in the absence of obvious signs. In 1925 if coliform urinary tract infections were suspected 'the exhibition of hexamine without results upon the pyrexia in three or four days gave a considerable presumption that the cause is not of this nature.' Alkalinization of the urine to relieve symptoms of urinary infection was well known to Horder 'if sodium bicarbonate in full doses also fails the presumption (of urinary tract infection) becomes the greater' but the assistance of this form of therapy is often neglected today.

Today the problem is not so much the diagnosis and treatment of urinary tract infection but deciding which patients ought to be further investigated.

The genital tract

Horder mentions therapeutic trials of arsenical compounds against spirochaetal conditions associated with fever – although surprisingly he was not so much concerned with syphilis as with rat bite fever! Concealed septic (criminal) abortion was not uncommon for many years after Horder's original paper but now, probably due to liberal abortion laws, septic abortions have now become uncommon. Of genital infections, herpes simplex, secondary syphilis, or invasive gonorrhoeal infections (salpingitis, septicaemia, or perihepatitis) may present as a PUO.

Reticulo-endothelial system

Horder remarked that 'neoplasms occasionally cause obscure pyrexia.' In his experience 'they are odd neoplasms, neoplasms which are prone to undergo necrosis . . .' Today it is unusual for neoplasms to be diagnosed only after they have reached a necrotic stage. He also mentions lymphadenomas, particularly those which are 'prone to involve deep-seated glands

or the lymphoid tissue in the viscera, without obvious glandular enlargement at all' as causes of a PUO. Today most of us are familiar with occult intra-abdominal Hodgkin's disease as a cause of PUO requiring sophisticated investigations and biopsies for diagnosis.

The blood

In 1925 'everyone gives quinine to the Anglo-Indian who has a shivering fit and a high temperature, headache, and sweats.' Today one usually likes to make the diagnosis of malaria before treatment commences, but if cerebral (*falciparum*) malaria is suspected one usually commences treatment before laboratory reports are available. It is of note that Horder's quinine, which does not prevent intrahepatic persistence of malarial parasites (presumably in those days Indian malaria would probably have been caused by *Plasmodium vivax* or *P. ovale*), would only have cured individual feverish episodes without preventing relapses, and this may account for the 'Old Soldier's' malaria which kept on returning despite treatment. Now additional primaquine solves the problem by eradicating the intrahepatic forms of the parasite.

Horder would have been aware of most of the disorders in Figure 1 but would probably have lacked the laboratory facilities to confirm his diagnosis. The disease of which he most certainly was aware was tuberculosis, and he remarked upon the difficulties surrounding the 'dark horse' groups of glands in the thorax and abdomen 'which cannot be very well, or at least not very convincingly, examined.' Investigatory techniques have changed and today one can usually tell if glands are abnormal although defining why they are abnormal may pose difficulties. He then went on to make an observation that some tests (in his example chest X-rays) may increase diagnostic problems rather than provide clarification – and which of us does not know this feeling? And to make a point of continuing poignancy he then alludes to the fact that in this situation most such patients are often relatives of doctors. Certain aspects of medicine have not changed in 60 years!

New diseases

In the last 60 years there has been increasing recognition of 'new' classes of infection-related diseases which can present as PUO.

Opportunistic infections

These are infections which attack patients whose underlying condition, or therapy, increases susceptibility to infection: there are many more patients

vulnerable from opportunistic infections today, largely because people survive for longer with various serious diseases and also because of the unfortunate side effects of immunosuppressant and cytotoxic drugs used for treating neoplastic conditions. Sir Thomas perhaps anticipated the development of opportunistic infections – ‘but we need not worry about the spontaneous disappearance of diseases; we can create others.’ (Horder, 1953). Opportunistic iatrogenic complications are not uncommon – 36 per cent of general medical patients in one paper (Steel *et al.*, 1981).

There are several patterns of infection recognized in various groups of immunocompromised patients. Patients with antibody defects often develop infection with bacteria rather than viruses, possibly due to reduced opsoninisation. Patients with defective phagocytic function often develop infection with extracellular bacteria, including their own commensal bacteria. Patients with defective (T) cell-mediated immunity may develop infections with facultative and obligate intracellular organisms because cell-mediated immunity is the main host defence against intracellular pathogens.

Patients with such defects are at increased risk of infection with both ‘standard’ and unusual organisms; they may not be able to mount an adequate inflammatory response or produce the normal signs of infection, including a polymorphonuclear response in the blood film. Despite this, such patients usually mount a febrile response to invasive infections, and the fever may be the only sign of infection.

Disorders such as the acquired immunodeficiency syndrome and its spectrum of opportunistic infections (Waterson, 1983), would have been unsuspected in 1925. Certainly one of the major predisposing factors, promiscuous male homosexuality, would not, and could not, have been openly acknowledged.

Zoonoses

These are diseases and infections which are naturally transmitted between vertebrate animals and man (WHO Expert Committee, 1982), and may often go unsuspected if the significance of an occupational history or history of animal contact is missed. In the past the main British PUOs affecting farm workers were brucellosis, leptospirosis, Q fever and tuberculosis, but now brucellosis has been eradicated from British cattle and tuberculosis has been rigorously controlled. Non-typhoidal salmonella infections, which are becoming more common in both animals and humans, may present atypically as PUOs without the clue of diarrhoea or vomiting.

New investigatory techniques

The blood, after the urine, is the most easily available body fluid for investigation. In 1925 tests were often

performed in ward side-rooms and no clinician would have been unfamiliar with a microscope. Today the support of a series of laboratories is an accepted part of medical care: thus ready communication is essential for the effective functioning of the team approach concept of modern medicine. The telephone service has developed since 1925 and advice from any authority is but a telephone call away. The ubiquitous bleep also ensures rapid communication (at the price of continual interruption!).

Microbiology

Provided that we submit appropriate specimens we now expect confirmation of infections whether by culture or by serological tests. In 1925 serology was in its infancy and it was only in 1942 that a virus, rather than a ‘non-filtratable agent’ was linked with a disease. Taking pneumonias as an example we can now suspect and confirm and (with the exception of cytomegalovirus infection) treat legionnaire’s disease, cytomegalovirus pneumonia, influenza, pneumocystis, psittacosis, Q fever or mycoplasma infections.

New investigations

There is now a veritable surfeit of investigations that can be ordered at the stroke of a pen. In the face of all this new technology we should not forget Horder’s remark in 1953 that ‘Fifty years ago . . . a consultant often took with him only his stethoscope (he had always with him, of course, the most valuable instrument of all, his brain and experience)’ (Horder, 1953).

Endoscopic visualization of the respiratory and gastro-intestinal tracts using rigid tubes would have been available to Sir Thomas, but the development of fibroptic technology has had a dramatic impact on patient investigation and management.

Perhaps Horder would have predicted that in 1985 no organ would be safe from the probing biopsy needle in search of histology, culture and sensitivity. He might also have predicted that the clinical technique of percussion would have become developed into ultrasound examinations which create sonic pictures of internal organs; he would no doubt have been aware that an ultrasound technique had been already used to investigate a body in 1912 – that of the Titanic at the bottom of the Atlantic.

Horder might have been aware that a microscope that used electrons instead of light was theoretically possible (it was first used in the late 1930s) but would he have predicted computers and their ability to synthesize X-ray sections in any plane of any bodily organ by computerized axial tomography, which became available in the early 1970s? Because of these modern techniques a blind ‘I’ve no idea what we might find’ laparotomy has become almost obsolete.

New therapies

Many new forms of therapy have been developed since 1925. As Horder remarked 'there are certain test drugs which I suppose, we all, at times, try in certain pyrexial cases.' He mentions quinine for malaria, salicylates as a test for acute rheumatism, and emetine for dysenteric and post-dysenteric pyrexial conditions, presumably the latter indication referring to extra-intestinal amoebic infection.

Particularly in ill neutropenic patients therapeutic trials of antibiotic therapy are undertaken today, whilst awaiting culture results. It is likely that today the most common therapeutic trial in PUO patients is for suspected occult tuberculosis, a disease which now particularly occurs in immigrants from Asia and, to a lesser extent, Africa. Drugs such as ethambutol and isoniazid in combination are particularly useful in such circumstances as they have no significant activity against non-tuberculous bacteria.

The powerful but occasionally treacherous corticosteroids are now used extensively for their anti-inflammatory and immunosuppressive properties in seriously ill patients who have not responded to other therapy – 'the last rites of the twentieth century' – whilst accepting that their use may delay diagnostic manifestations of underlying infection.

Travel

The patterns of illness that can cause a PUO have not been static over the past 60 years, and neither have the patients. Given a large enough bank balance it is possible to be transported almost anywhere on earth within 36 hours. Given a large enough bank balance and a good enough reason it is even possible to travel into space – but one hopes that Professor Hoyle's belief in viruses from space (Hoyle, 1983), does not prove correct and provide us with other infectious causes of PUO to vex us in the future!

In Horder's day many patients with serious tropical infections would have fallen ill well away from England's green and pleasant land, and probably would have died either where they contracted their infection or were buried at sea on the return journey, but in this age of rapid intercontinental air travel every doctor has to have a working knowledge of the common or serious tropical infections.

Notable fevers derived from the Tropics

Falciparum malaria

Although termed malignant tertian malaria because the fever in established cases occurs every third day it is

important to realize that initially the fever can be totally without pattern. It is equally important to realize that adequate prophylaxis does not exclude malaria as a diagnosis, and that any febrile illness, no matter what the manifestations may be, might be malaria. The other types of malaria (*P. vivax*, *P. ovale*, or *P. malariae*) may present with almost any incubation period, especially if ineffective prophylaxis has been taken.

Typhoid fever

This is now usually an imported infection although in the past indigenous typhoid was common. Initially symptoms are vague with fever, abdominal discomfort, splenomegaly, constipation, a dry cough, and rose spots, if seen, are suggestive. Diagnosis depends on culture of the causative organism: serological tests may be unhelpful or misleading (particularly in the vaccinated) (Brodie, 1977), an occurrence previously noted by Horder. Other non-typhoidal salmonella infections may present with an enteric fever picture.

Amoebiasis

To cause a PUO, infection has to be invasive, usually involving abscess formation. Abscesses occur in extra-intestinal situations, commonly in the liver, when they may be associated with obscure fever: only in the later stages does rib tenderness and hepatomegaly result. Ultrasound and serological tests may both contribute toward a correct diagnosis.

Tuberculosis

Tuberculosis is still common in certain parts of the world and recent immigrants, returning travellers, or their children may be at risk.

Hepatitis

In the prodromal periods before jaundice develops both hepatitis A and hepatitis B can present with fever and constitutional illness. Patients may become ill in the prodromal period of hepatitis but may not become jaundiced. Yellow fever should not be forgotten as a cause of a febrile hepatitis.

Leptospirosis

The diagnosis is easy if the classical Weil's syndrome results with sudden onset of headache, meningism, haemorrhagic lesions, jaundice, or conjunctival injection. However, the spectrum of illness produced by leptospire is wide and diagnosis might have to rely on serological tests if the clinical picture or occupational history is suggestive.

Typhus

This is occasionally imported today: Horder would have been familiar with epidemic (louse borne) typhus which had taken a considerable toll during the First World War.

Pulmonary embolism

Prolonged air journeys with seat pressure on the calves is a well recognized cause of deep venous thrombosis and secondary pulmonary embolism: occult pulmonary emboli may cause fever in the absence of other symptoms.

Problem fevers derived from the Tropics: 'diseases of rapid travel'

Patients who have fallen ill with PUO within three weeks of return from bush areas of West Africa deserve special mention as there is the possibility of transmissible viral haemorrhagic fevers (VHF) which require special facilities for investigation and treatment (Emond, 1976). There are three African derived VHFs of importance: Lassa fever, Ebola virus disease, and Marburg virus disease. Lassa fever provides the most common importation and the most common VHF suspects that present in Britain (Emond *et al.*, 1978).

Lassa fever should be suspected in patients who have visited small towns or country areas in Western or Central Africa within the three weeks prior to the start of their illness, and considered to be a strong possibility in febrile patients who have been living or working in rural areas, medical and nursing staff from country hospitals, contacts of known cases, and laboratory workers handling dangerous materials within three weeks prior to the onset of illness (Emond *et al.*, 1978). These suspects need to be investigated under conditions of maximum security in special units. Whilst Sir Thomas Horder would be well aware that certain patients have to be barrier nursed I am sure he would not have predicted that patients with dangerous infections could be nursed in the sophisticated polythene bag known as a Trexler isolator (Hutchinson *et al.*, 1978).

PUO: the next 60 years

It is easy to review the immense progress that has been made in the last 60 years but what will the future bring?

The future will certainly bring even more expensive investigations! When Sir Thomas Horder stated that PUO presents a problem which 'taxes one's resources to the utmost' he was then referring to the challenge to

a physician's acumen, but this same comment could now be applied to the costs of modern investigation of a puzzling PUO.

New diagnostic techniques will emerge resulting in a proliferation of tests that could be performed.

Monoclonal antibody techniques will be further developed to enable rapid diagnosis of many infectious and non-infectious diseases, and tests for markers of infection and neoplasia using monoclonal antibodies will become widely available.

Scanning techniques will be developed which will supercede the CAT scan: nuclear magnetic resonance could be merely the harbinger of even more sophisticated (and expensive) investigations. Monoclonal antibody labelled with radioactive markers will enable specific target cells to be scanned.

New therapies will emerge relevant to the management of PUO. I would predict that:

1. Whole new classes of antibacterial agents will be discovered to replace the current obsessive modifications of side chains.
2. With antiviral substances including acyclovir (specifically for herpes infections) and interferon (at great cost) as a non-specific antiviral agent, the therapeutic antiviral revolution has only just commenced.
3. Monoclonal antibodies will enable specific attacks to be made against specific pathogens.
4. New vaccinations and other public health interventions will prevent certain infections and may cause others to die out because of a lack of susceptible subjects.
5. In future microorganisms will be developed which will specifically attack other microorganisms and neoplasms.
6. More new diseases will develop as the result of progress in medical treatment and techniques. Post-transfusion cytomegalovirus infection in renal transplant recipients would have been unknown in Horder's day!
7. Non-toxic treatments for serious diseases will be developed such that there will probably be more, rather than less, empirical treatments being used for feverish patients and if the treatment is not correct I have no doubt that the unravelling of the cause will be even more difficult.

Meanwhile the behaviour of whole populations will continue to change, not necessarily for the better. People will live longer, travel will become easier and cheaper, drug addiction may become even more of a major problem, and the sexual revolution will probably continue (albeit modified by the threat of the acquired immunodeficiency syndrome).

Unfortunately I have to conclude this review by predicting that the ever versatile microorganisms will

never surrender completely and will continue to evolve fresh challenges for the medical profession. I predicted above that microorganisms would be developed which would (therapeutically) attack other microorganisms. However, microorganisms have already used a similar ploy by producing the virus associated with the acquired immunodeficiency syndrome – which des-

troys cell mediated immunity allowing their colleagues – other intracellular organisms – to opportunistically and relentlessly attack some of those infected with the virus.

The future of PUO as a clinical problem is assured. Microorganisms will not let us rest. Perpetual vigilance will be mandatory.

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