CLINICAL MEDICINE AND THERAPEUTICS. II

EDITED BY PETER RICHARDS AND HUGH MATHER

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Clinical Medicine and Therapeutics. II

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Preface

The first volume of *Clinical Medicine and Therapeutics* was not designed to be comprehensive. The editors concentrated upon an approach to diagnosis and treatment in fields of current interest based firmly upon what it is sensible to do rather than upon an encyclopaedic account of what can be done. Pathogenesis was included where it illuminated treatment. The topics chosen were designed to interest and inform aspiring physicians preparing for their MRCP examinations and hopefully their senior colleagues as well.

Our purpose seems to have been achieved and we have been prompted to compile a second volume. Unlike the first, which was mainly written around contributions to a postgraduate course in medicine, this volume has been entirely purpose-built. Only three of the current authors contributed to the first volume and the topics presented here are different. Most of the authors are from St George's Hospital, London, but several chapters have been commissioned from outside; we have chosen topics of current concern, most of which are changing rapidly.

We hope that this volume will complement the first, and that together they will promote balanced judgement in reaching decisions of diagnosis and management.

Peter Richards
Hugh Mather

London 1979

Contents

CHAPTER 1

Pitfalls in the diagnosis of pyrexia of unknown origin

H. P. Lambert

INTRODUCTION

The very phrase, pyrexia of unknown origin, PUO (or FUO, fever of unknown origin, as commonly used in America), denotes a diagnostic enigma. Its solution is often a slow process, dogged with pitfalls. Few diagnostic processes can be so rewarding, and few so demoralising for patient, family and physician.

Definition of PUO is arbitrary. One well-known analysis by Petersdorf and Beeson (1961) included patients who had histories of fever for more than 3 weeks, which had defied diagnosis during the first week of study in hospital. Without formalising a definition in this way, the many transient fevers unaccompanied by signs of serious illness so commonly experienced without medical intervention and usually attributed to 'virus infection' will nevertheless not be discussed here. The causal diagnosis of these short-lived illnesses is sometimes achieved in the course of epidemiological studies involving virological methods, but rarely in ordinary medical practice, whether in community or in hospital, and innumerable illnesses of this sort still defy diagnosis. By contrast, and contrary to popular belief, obscure fevers lasting longer than 7–10 days (in patients not suffering from immune suppression) are rarely caused by viral infection. Viral infection can certainly cause prolonged fever, but rarely without other features which take the problem out of the PUO category. After the first week even the longest prodrome of measles or of smallpox will have been succeeded by the eruption, the prodrome of hepatitis has been followed by clinical and biochemical signs of liver disease, and the nodes, spleen and sore throat of infectious mononucleosis will have declared themselves. One exception is seen in cytomegalovirus infections which may show a characterless fever for 2 or 3 weeks, although investigation will soon reveal the lymphocytosis, disturbed liver function and specific serology.

PITFALLS WITH SYMPTOMS

Again by definition, symptoms in PUO do not reveal the cause of the fever,

but patients with fever certainly have symptoms and some of them can lead the clinician along false diagnostic paths. Among them note especially dysuria, common in women especially who are febrile even when, in the event, no evidence of urinary tract infection is forthcoming. Although headache as a dominant symptom may be significant, many individuals suffer headache with a fever independently of its cause. The aching limbs so common in fever may be falsely identified as specific arthralgia. Absence of symptoms too, may be a pitfall, as in nonbacterial pneumonias, when the sometimes total absence of any respiratory symptoms in the first few days may direct attention from the lungs as a possible focus of disease. Contrariwise cough as a fairly common symptom in typhoid may wrongly point to the lungs as the source of the PUO.

False localising symptoms are especially common in the gastrointestinal tract, since many patients with fever feel nauseated and vomiting commonly accompanies rigors of whatever origin. Constipation is so common in patients with fever as to be almost valueless in diagnosis, but more deceptive is the diarrhoea which can occasionally be a major feature of septicaemia, both coccal and Gram-negative, in patients who do not have identifiable bowel disease and in whom the origin of the septicaemia lies elsewhere than in the bowel. Careful analysis of abdominal symptoms is especially important since the possibility of laparotomy as a diagnostic measure is sometimes considered, and over-interpretation of abdominal symptoms may lead to a futile exploratory operation.

Another important pitfall in history-taking is to miss out on a full list of previous medications, since drug fevers are not uncommon, may occur in association with a vast number of agents, and may continue indefinitely without familiar clinical pointers such as rashes or pruritus. It is astonishing how many times a patient may be interviewed without, by accident or design, revealing an important potential cause of fever. "Oh yes, I've been on methyldopa for years", or "I was put on warfarin after that thrombosis at 'St Elsewhere's' 10 years ago; I only go for a blood test every six weeks."

Finally, where has the patient been in recent weeks and months, and what is his job? The recurrent tragedies from *falciparum* malaria have been too widely publicised to need repetition here, but misconceptions about the supposed absence of malaria from some areas of the world persist, while occupation-exposure to allergens as a cause of recurrent fever is easily overlooked.

PITFALLS WITH SIGNS

The temperature chart. It cannot be denied that patients are seen with tertian fever who have *vivax* malaria, with stepladder temperature chart and slow pulse who have typhoid or with spiking intermittent fever who have deep abscesses or cholangitis. Patients with brucellosis may even have undulant fever. But these 'classical' examples are usually much outnumbered by less

characteristic charts, and the most common pitfall in PUO is over-reliance on the shape and character of the temperature chart. One of the 'characteristic' charts should be regarded as a bonus point in diagnosis, but its absence should never be taken to exclude the diagnosis supposedly characterised by the particular type of fever. This potential mistake has its greatest importance in malaria. The temperature chart does not show regular periodicity early in the illness and may never take on the textbook character. The only safe rule is to consider malaria in anyone who is ill, with or without a fever, from a malarial area. Remember too that drugs may both cause fever and influence an existing fever. The chart of a patient with typhoid may be converted by a few doses of aspirin into a dramatic series of spikes suggestive of hidden pus rather than enteric fever.

Rigors are disappointing as a diagnostic clue. They may be seen in a large number of fever-causing illnesses. Some of the most dramatic are seen in severe mumps when they may, by a day or so, precede the orchitis which they often herald, and lead to a diagnosis of bacterial septicaemia, a suspicion fostered by the neutrophilia also found. Rigors may become prominent as a result of salicylate administration in fever of various causes.

In the nervous system the most common difficulty is establishing the distinction between delirium or nonspecific confusional states associated with fever, and neurological features indicating specific involvement of the CNS. Useful pointers here are that delirium is associated in time with the fever, but not with signs of raised intracranial pressure or with focal CNS signs.

Meningism, in the sense of stiff neck with or without Kernig's sign in a patient whose CSF is normal, is a common event in systemic infection, especially in school-aged children and young adults. It may be observed in any patient with high fever, but is particularly common in pneumonia (allegedly of the upper lobes, but found in fact with any pneumonia), bad tonsillitis and influenza. Occasional associations are the early phase of typhoid fever, which may also show encephalitic features, and meningism is rarely seen in the prodrome of hepatitis. Neck or back stiffness from spinal osteitis is a rare local cause.

Another rare but important neurological pitfall is the combination of headaches, not always very severe, and prolonged low fever as sole manifestations of late secondary syphilis. The headache may be mild enough to be considered a non-specific symptom, but serum and CSF serology will make a diagnosis important for the future of both patient and contacts.

Although often an invaluable diagnostic lead, jaundice may also provide a deep pitfall in the diagnosis of PUO. Disturbed liver function is a common feature in many generalised infections, especially in pyogenic septicaemias and in patients with a background of alcoholism or liver disease. The serum bilirubin may be high enough to make jaundice a prominent feature, but especially deceptive are those few patients with a cholestatic biochemical pattern which leads to a false diagnosis of biliary obstruction. Such patients

may have septicaemia from pelvic sepsis or appendix abscess and there may, at laparotomy, be no evidence of portal pylephlebitis, of cholangitis or of liver abscess.

PITFALLS WITH INVESTIGATIONS

An operational policy for the investigation of PUO will be proposed at the end of this chapter, but first, pitfalls in investigation need to be revealed.

White cell counts

In afebrile patients the white cell count ranks with estimation of the plasma proteins as the most commonly performed investigation yielding nothing to advance the diagnostic process. In a patient with fever, by contrast, this is one of the major diagnostic signposts. Neutrophilia is not characteristic of infection in general, but rather of pyogenic infection, whether by Gram-positive cocci, Gram-negative cocci or pyogenic Gram-negative rods such as the coliforms or by anaerobes. It is also found, however, in some nonbacterial infections (especially important in the context of PUO are amoebiasis and leptospirosis) and also in many noninfective processes. Note especially tissue damage from any cause, haematomas, thromboembolism, liver necrosis, polyarteritis (sometimes) and juvenile rheumatoid arthritis (commonly). Contrariwise, the total white cell count may be normal or low in pyogenic infection, especially in patients with serious disease of sudden onset and in alcoholics. The differential count then shows shift to the left and toxic granulation, and pyogenic infection is rightly suspected.

Blood culture

The pitfalls are well known. Good technique, proper skin cleansing, use of anaerobic as well as aerobic media, prolonged incubation, use of 10% CO_2 and sometimes of special media (eg when brucellosis is suspected), will prevent most mistakes. Timing of blood cultures has been much discussed but perhaps overemphasised since bacteraemia, when present, is more constant than was formerly supposed. With irregular fevers, however, blood cultures should be taken soon after the temperature begins to rise.

Serology

Serological tests may be very important in establishing a diagnosis in conditions such as brucellosis and leptospirosis in which isolation of the organism is not commonly achieved or, as in rickettsial infection, is dangerous to attempt except in special category laboratories.

Nevertheless, serological tests, especially tests of serum agglutinins, are

commonly misinterpreted, especially in typhoid, paratyphoid and other salmonelloses. Serological changes counted as evidence of current infection are often attributable to previous immunisation or to subclinical exposure in areas of high salmonella prevalence. More generally, it is easy to forget that the favoured 'four-fold rise' signifies a shift of only two dilutions in a standard series, and should be interpreted with reserve as sole evidence of infection by the organism concerned. Many attributions of prolonged fever to viral infection are based on this type of inadequate evidence.

The operational plan

How can the pitfalls be avoided and the diagnosis made with as much speed and as little risk as possible? The best approach is to pursue an explicit operational plan with the following steps.

1 Detailed, including geographical and occupational, *history and physical examination.*

2 *'First round' investigations.* The essentials are full blood count, blood culture, midstream urine for microscopy and culture, and plain film of the chest. Serum should be saved for future use and any other initial investigations made which are indicated by available clinical data.

3 *'Second round' investigations.* If initial assessment fails to reveal the diagnosis and the illness continues, three steps are now necessary, which may themselves be repeated if the diagnosis remains elusive:

(a) Take the history and examine the patient again. Protracted PUO is so demoralising to patient and doctor that basic clinical rules may unwittingly be flouted, especially the need for a general and total re-assessment as time passes. It may thus be found that pelvic examination, not repeated since admission many weeks before, now reveals a mass, re-examination of the fundi may show new embolic lesions or choroidal tubercles, or in a previously normal heart may now be heard the faint murmur of aortic incompetence. The answer to a PUO may as often be found by re-examination as by more and more elaborate investigations.

(b) Repeat the simple 'first round' and noninvasive investigations.

(c) Proceed to more complex tests. At this point the range of possible investigations is so great that blind or nonspecific investigation becomes impossible. Now the whole range of diagnoses must be reviewed and, however difficult it may be, a further order of investigation agreed. Although the diagnostic pathway has, in larger centres, been so much changed by modern imaging techniques, many patients with PUO are seen where these methods are not available, so it is well to remember the diagnostic methods which do not depend on them. Among the most important are *serological tests*, bearing in mind the

reservations already made, for infections such as brucellosis, salmonelloses, leptospiroses, amoebiasis and rickettsial diseases; simple radiology of the renal and gastrointestinal tract; and especially, the value of *biopsy* of any available tissue for microbiological and histological examination. The most useful tissues are the liver, lymph nodes and bone marrow, and the relevant laboratories should be consulted in advance to avoid mistakes in handling biopsy material which may diminish its value.

The rapid advances in new methods of *diagnostic imaging*, especially of ultrasound and radionucleide techniques, have quietly revolutionised many aspects of diagnosis and have greatly modified the decision pathway involved in analysing PUO. It is interesting to speculate how many difficult problems of PUO have become soluble by these noninvasive investigative methods. The role of each has yet to be fully assessed and can be briefly indicated. Ultrasound has its greatest potential in seeking out local abnormalities of the liver, gall bladder and pancreas, in the detection of stones and dilatation of the bile ducts, in the detection of pelvic and prostatic abnormalities, and in expert hands, identification of cardiac vegetations. Of the many radionucleide techniques, those of greatest potential in PUO are technetium-99 phosphate scanning of bone as a much more sensitive indicator of infection than standard radiology, gallium-67 scanning to detect inflammatory masses and isotope scanning of the liver, usually with technetium-99 sulphur colloid to detect many diffuse and focal abnormalities. The place of computerised axial tomography in diseases of the brain and orbit is fully established, but 'whole body scanners' are not yet generally available, nor is their value in relation to other techniques yet thoroughly explored. It is already evident, however, that this and other new imaging methods may greatly improve diagnostic accuracy in several anatomical regions important as sites of PUO, especially the retroperitoneal spaces, pancreas, mediastinum and lymph nodes.

These techniques, like all others, have their own pitfalls, but their advent means that painful and dangerous investigations may now often be avoided in patients with PUO. Thus, lymphangiography is now indicated less commonly than formerly but, above all, *laparotomy*, formerly a last ditch manoeuvre in the most intractable problems of PUO, should now rarely be entertained without positive evidence of intraabdominal or pelvic pathology.

Therapeutic tests

Therapy on a 'best guess' hypothesis often has to be started when the patient is too ill, or declining too rapidly, for treatment to wait upon a proven diagnosis. The physician strives to avoid both the tragedy of waiting too long, and the confusion and sometimes harm which results from multiple therapies in patients who present a difficult diagnostic problem but are not very ill; 'fever

alone is no cause for hurry'. More positively, specific treatments are occasionally valuable as diagnostic tests. Isoniazid for presumed tuberculosis in Asian patients with PUO in whom no material for biopsy can be found, or when biopsies are unhelpful, heparin for fever of thromboembolism, chloroquine for presumed malaria (not quite specific since amoebiasis would also be affected) and colchicine for familial Mediterranean fever are examples of such therapeutic tests. The most common test of value in this respect is, however, the converse one, withdrawal of a drug to test its role as a cause of prolonged fever.

A few special problems

Tuberculosis

In Asian patients tuberculosis often presents as a featureless PUO. The sites of disease are to be found in mediastinal or abdominal nodes, in the uterus and ovaries, in the serous cavities and omentum or in the bowel, while in the early stages of tuberculous meningitis there may be surprisingly few pointers to the CNS in the symptoms and signs.

Arteritis

In elderly people the polymyalgia–polyarteritis syndrome may present as a PUO especially difficult to solve, since the patient's poor condition and high ESR leads to justifiable suspicion of malignancy and full investigation may reveal no suitable biopsy site; the futility of blind muscle biopsy is often confirmed in the course of investigation. Histological diagnosis is sometimes made from the temporal artery or by renal biopsy, but a trial of steroids may be justified when this diagnosis is strongly suspected but unproved.

Factitious Fever

The dramatic and often unsuspected nature of factitious fever leads to a greater emphasis on this diagnosis than its rarity justifies. The patients, often members of nursing or other professions related to health care, cause so much drama in their environment that most doctors find them unforgettable, and cherish the illusion that factitious fever is a common cause of PUO. Two different methods are involved, one the falsification of temperature measurements, the other production of real fever by, self-injection of vaccines or faecal material. Both may be concealed with baffling ingenuity, and staff caring for them may hotly deny such an interpretation of the illness. Direct confrontations are rarely helpful and progress is best made by a positive and tactful approach to the underlying psychological problems, while attempting to identify and then remove the means by which fever is being induced.

CHECK-LIST OF CAUSES

The following check-list may help to remind the reader of the diagnoses which have been made with greater or less frequency in prolonged PUO.

1 *Infections*

(a) Localised, for example abscesses, especially of subphrenic, intrahepatic, pelvic, perinephric and other retroperitoneal sites.
Subacute bacterial endocarditis.

(b) Generalised, for example tuberculosis, brucellosis, salmonellosis, malaria, rickettsial infection, cytomegalovirus and systemic mycoses.

2 *Neoplasm*

Usually lymphoma, less often carcinoma and occasionally benign tumour especially of stomach or uterus.

3 *Collagen disease*

(a) Polyarteritis.

(b) Juvenile rheumatoid arthritis in its sometimes prolonged prodromal phase.

(c) Rheumatic fever especially in relapse.

(d) SLE before specific tests have become positive.

4 *Vascular disease*

Thromboembolism and multiple pulmonary emboli.

5 *Drug fever*

6 *Liver disease*

Chronic hepatitis/or chronic active hepatitis. Granulomatous disease of the liver, often without known associations of liver granuloma such as tuberculosis, sarcoid and syphilis.

7 Disorders of haemopoiesis, especially myeloma, and paraproteinaemias.

8 Bowel disease without bowel symptoms, especially Crohn's disease and Whipple's disease.

9 Sarcoidosis.

10 Thyroid disease, subacute thyroiditis, hyperthyroidism.

11 Familial Mediterranean fever.

12 Factitious fever.

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