

Seminar

Fever of unknown origin

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Diagnosis often involves pattern recognition—for example, thyrotoxicosis or rheumatoid arthritis commonly have a constellation of distinctive clinical features and laboratory tests are then done for confirmation. This approach is more difficult when the clinical features are few, subtle, or insufficient to characterise a disease or group of diseases. Diagnosing the cause of fever is sometimes like this, and the most perplexing of such cases are grouped under the heading fever (or pyrexia) of unknown origin (FUO). These cases are encountered once or twice a month at teaching hospitals.¹⁻⁴

FUO defies simplification. Reported causes exceed 200 (panel 1), and fall into diverse sub-specialty categories. There are no algorithms and few clues that reliably suggest or exclude particular diagnoses. The clinician must rely on very careful evaluation and detailed knowledge of a wide variety of diseases.

Definition

FUO means fever that does not resolve spontaneously in the period expected for self-limited infection and whose cause cannot be ascertained despite considerable diagnostic effort. In 1961, Petersdorf and Beeson⁵ introduced the definition that subsequently became standard—namely, illness of more than three weeks' duration, fever higher than 38.3°C (101°F) on several occasions, and diagnosis uncertain after one week of study in hospital. Because hospital admission is so expensive and since thorough diagnostic testing now can be done in outpatient settings, the definition recently was modified to remove the requirement that hospital be the setting for a week of evaluation.^{6,7} The definition does not specify what constitutes this evaluation but the studies listed in panel 2 are, we suggest, the minimum.

Recognition that the causes of unexplained fever in patients with impaired immunity may differ from those in classic FUO has prompted categories such as FUO in cancer^{8,9} for FUO in HIV infection,¹⁰ groupings that help formulate a more relevant and economical differential diagnosis, as has also been done with FUO in elderly patients¹¹ and children.¹²⁻¹⁴

Causes

The proportion of FUO cases grouped in specific disease categories has changed little during the past four decades (panel 3). Infection accounts for about one-third of cases, followed by neoplasia and collagen vascular diseases. The frequency of neoplasia declined in several recent series^{2,3,19}

ostensibly due to improved diagnostic imaging,² but in a contemporaneous series the proportion was 24%.⁶ In our hospital neoplasia, in particular lymphoma, remains an important cause of FUO.

The role of certain individual diseases has changed considerably. For example, rheumatic fever and systemic lupus erythematosus (SLE) were common in early series but are unusual today, probably because of the sharp decline in rheumatic fever in the developed world and the wide availability of accurate tests for SLE that permit early diagnosis. Infective endocarditis has decreased in frequency since the 1950s as blood culture techniques have improved, but new pathogens that are difficult to isolate (eg, *Bartonella quintana*) ensure that it will not disappear as a cause of FUO. A few diagnoses in recent series were unknown four decades ago, including Lyme disease, acute HIV infection, Sweet's syndrome, and *Bartonella* endocarditis. Early series also failed to report drug fever as a cause of FUO.

Diagnosis

The diagnostic approach in FUO has not been uniform but has always included a thorough history, careful physical examination, laboratory tests, and radiographic studies. These modes of investigation interact so the contribution of each to a diagnosis is difficult to assess, even when the method of diagnosis or yield of a specific test is reported.^{1-6,11,19} The difficulty is reflected by the interval between hospital admission and diagnosis, which averaged 19 days in two recent studies.^{2,6}

The causes of FUO are usually familiar diseases with uncommon presentations rather than rare disorders. In several series of paediatric^{12,14} and adult⁶ cases the correct diagnosis was possible from the history, physical examination, and routine laboratory tests. Conversely, failure to utilise findings correctly,^{13,14} delay in ordering appropriate tests,² and misinterpretation of test results¹² have all contributed to missed diagnoses. Specialised non-invasive tests such as serology seldom help except to confirm a diagnosis suggested by other findings.

History

A thorough history is important,^{16,20,21} and this should include information about alcohol intake, medications, occupational exposures, pets, travel, familial disorders, and previous illnesses. Examples of diseases for which clues were provided by the history include amoebiasis (foreign travel), familial Mediterranean fever (family history), psittacosis (contact with parakeets), metastatic cancer (previous primary cancer), and drug fever (medications). Awareness of prior inflammatory processes in the abdomen is especially important; in a recent series, 8 of 9 patients with FUO due to intraabdominal abscesses had Crohn's disease or a prior episode of cholecystitis, diverticulitis, or appendicitis.⁴ Specific

Lancet 1997; **350**: 575-80

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complaints have not always been helpful. Only about one-half of the patients with abdominal complaints and about one-fourth of those with central-nervous-system complaints had disease at the corresponding site.^{14,15}

Physical examination

The specific findings that have led to a diagnosis in FUO are numerous and diverse. Examples included slight enlargement of the thyroid (thyroiditis), periodontal disease or loose teeth (dental abscess), thickened temporal artery (temporal arteritis), cardiac murmur that changes with position (atrial myxoma), and widespread hyperpigmentation (Whipple's disease). The key findings can often be detected only by a very careful examination

and may be missed first time. Illustrating the embarrassment that can arise from an incomplete examination is a patient whose wound abscess at an amputation stump was concealed by a prosthesis and was missed by at least four different specialty services.¹

The yield of the physical examination is not recorded in most studies of FUO, other than to note that diagnostic testing often was guided by abnormalities detected in the initial evaluation. That the yield may be high is suggested by two studies reporting that in paediatric patients about 60% had abnormal findings that contributed to a diagnosis.^{13,14} In half of these cases, the abnormalities were detected only by repeat examinations.¹⁴ Lymphadenopathy, which might be considered an important finding, generally has not correlated with specific illnesses or a positive biopsy.^{13,15}

Panel 1: Causes of FUO*

Infection

Intraabdominal abscess (eg, periappendiceal, diverticular, subphrenic); liver, splenic, pancreatic, perinephric, psoas, or placental abscess

Appendicitis, cholecystitis, cholangitis, aortoenteric fistula, mesenteric lymphadenitis, tubo-ovarian abscess, pyometra

Intracranial abscess, sinusitis, mastoiditis, otitis media, dental abscess

Chronic pharyngitis, tracheobronchitis, lung abscess

Septic jugular phlebitis, mycotic aneurysm, endocarditis, intravenous catheter infection, vascular graft infection

Wound infection, osteomyelitis, infected joint prosthesis, pyelonephritis, prostatitis

Tuberculosis, *Mycobacterium avium* complex, leprosy, Lyme disease, relapsing fever (*Borrelia recurrentis*), syphilis, Q fever, legionellosis, yersiniosis

Salmonellosis (including typhoid fever), listeriosis, *Campylobacter*, brucellosis, tularaemia, bartonellosis, ehrlichiosis, psitticosis, *Chlamydia pneumoniae*, murine typhus, scrub typhus

Gonococcaemia, meningococcaemia

Actinomycosis, nocardiosis, melioidosis, Whipple's disease (*Tropheryma whippelii*)

Candidaemia, cryptococcosis, histoplasmosis, coccidioidomycosis, blastomycosis, sporotrichosis, aspergillosis, mucormycosis, *Malassezia furfur*, *Pneumocystis carinii*

Visceral leishmaniasis, malaria, babesiosis, toxoplasmosis, schistosomiasis, fascioliasis, toxocariasis, amoebiasis, infected hydatid cyst, trichinosis, trypanosomiasis

Cytomegalovirus, HIV, *Herpes simplex*, Epstein-Barr virus, parvovirus B19

Neoplasia

FUO has been reported in association with all common malignant diseases, and with 46 altogether

Collagen vascular disease

Adult Still's disease, SLE, cryoglobulinaemia, Reiter's syndrome, rheumatic fever, giant cell arteritis/polymyalgia rheumatica, Wegener's granulomatosis, ankylosing spondylitis, Behçet's syndrome, polyarteritis nodosa

Hypersensitivity vasculitis, urticarial vasculitis, Sjögren's syndrome, polymyositis, rheumatoid arthritis, erythema multiforme, erythema nodosum, relapsing polychondritis, mixed connective-tissue disease, Takayasu's aortitis, Weber-Christian disease, Felty's syndrome, eosinophilic fasciitis

Miscellaneous

Haematoma, thrombosis, recurrent pulmonary embolism, aortic dissection, femoral aneurysm, post-myocardial infarction syndrome, atrial myxoma

Drug fever, Sweet's syndrome, familial Mediterranean fever, familial Hibernian fever, hyperimmunoglobulin D syndrome

Crohn's disease, ulcerative colitis, sarcoidosis, granulomatous hepatitis

Subacute (de Quervain's) thyroiditis, hyperthyroidism, adrenal insufficiency, primary hyperparathyroidism, hypothalamic hypopituitarism, autoimmune haemolytic anaemia

Gout, pseudogout

Cirrhosis, chronic active hepatitis, alcoholic hepatitis, shunt nephritis

Malacoplakia, Kawasaki's syndrome, Kikuchi's syndrome

Mesenteric fibromatosis, inflammatory pseudotumour

Castleman's disease, Vogt-Koyanagi-Harada syndrome, Gaucher disease, Schnitzler's syndrome, FAPA syndrome (fever, aphthous stomatitis, pharyngitis, adenitis), Fabry's disease

Cholesterol emboli, silicone embolisation, Teflon embolisation

Lymph node infarction, sickle cell disease vasoocclusive crisis, anhidrotic ectodermal dysplasia, cyclic neutropenia, Brewer's yeast ingestion, Hamman-Rich syndrome

Milk protein allergy, hypersensitivity pneumonitis, extrinsic allergic alveolitis, metal fume fever, polymer fume fever, idiopathic hypereosinophilic syndrome

Complex partial status epilepticus, cerebrovascular accident, brain tumour, encephalitis

Anomalous thoracic duct, psychogenic fever, habitual hyperthermia, factitious illness

*Identified in case-reports and case series published during 1961-97.

Clinical features

Although it is logical to try to narrow the differential diagnosis in individual cases of FOU by focusing on specific clinical features, this approach has helped little. Fever has been characterised by magnitude and frequency, and specific fever patterns have been ascribed to many of the causes of FOU.²² Unfortunately, in most case series, the height, pattern, or duration of fever did not relate to diagnosis.^{3,13-15} The few entities that usually have a distinctive fever pattern (eg, non-falciparum malaria or cyclic neutropenia) are rare, and fever patterns thought to be distinctive for other diseases, such as Pel-Ebstein fever in lymphoma, are seldom seen. Relative bradycardia may be useful when present, although it is associated with a substantial differential diagnosis, including typhoid fever, legionnaire's disease, psittacosis, leptospirosis, drug fever, brucellosis, subacute necrotising lymphadenitis, neoplasm and factitious fever. The response of fever to naproxen sodium may be helpful in that fever due to solid tumours and many rheumatological diseases (most notably Still's disease) usually subside promptly while fever due to other causes may persist.^{23,24} Other features, such as sweats, chills, or weight loss have not discriminated among causes of FOU. The generalisation that FOU of very long duration is unlikely to be due to infection is fairly reliable but applies to few patients.

Laboratory tests

Non-invasive laboratory tests have provided a diagnosis in perhaps one-quarter of FOU cases.^{6,18,19} These include serological tests for microbial pathogens or rheumatological diseases. Paradoxically, the role of enhanced culture systems in diagnosing cases of FOU is probably diminishing because the commercial systems that are now widely used are excellent at recovering fastidious bacteria, mycobacteria, or fungi before the conditions for FOU are met.

Imaging has been used primarily to localise abnormalities for subsequent evaluation. Computed tomography (CT) of the abdomen, in particular, has increased the rate of positive results when subsequent invasive diagnostic procedures are done.²⁵ Structures that appear abnormal by CT are almost always confirmed by laparotomy or biopsy to be abnormal.²⁶ The usefulness of abdominal CT and occasionally ultrasound scanning of the gallbladder and hepatobiliary system has resulted in application of these tests to virtually all cases of FOU.

Panel 2: Minimum diagnostic evaluation to qualify as FOU

Comprehensive history
Repeated physical examination
Complete blood count, including differential and platelet count
Routine blood chemistry, including lactate dehydrogenase, bilirubin, and liver enzymes
Urinalysis, including microscopic examination
Chest radiograph
Erythrocyte sedimentation rate
Antinuclear antibodies
Rheumatoid factor
Angiotensin converting enzyme
Routine blood cultures (×3) while not receiving antibiotics
Cytomegalovirus IgM antibodies or virus detection in blood
Heterophile antibody test in children and young adults
Tuberculin skin test
CT of abdomen or radionuclide scan
HIV antibodies or virus detection assay
Further evaluation of any abnormalities detected by above tests

Because of their extensive use, tabulated in one study at more than three CT and/or ultrasound examinations per patient,² the yield per test has been only about 10%.^{2,11,27} False-negative CT results have occasionally been reported, even with abscesses in solid organs, due to distortions of normal anatomy, small abscess size, or failure to use both oral and intravenous contrast agents. In adults, the failure of ultrasound to detect many liver, spleen, and intraperitoneal abscesses precludes reliance on this examination.

Scanning with gallium-67 or indium-111 labelled autologous leucocytes has been helpful when infection or malignancy is the cause of FOU, and the overall yield may be higher than that with CT or ultrasound.^{27,28} Positive results also have been reported with diverse diseases including sarcoidosis, localised Castleman's disease, thyroiditis, and giant-cell arteritis. Limitations include false-negative gallium results with secondary infected lesions (eg, haematomas or pseudocysts) difficulty detecting splenic abscesses due to a high level of background uptake in the spleen, and a low positive predictive value with indium. A promising new radiopharmaceutical, indium-111-labelled immunoglobulin, appears very sensitive for the detection of focal infection,^{29,30} and its eventual role in FOU probably hinges on its accuracy in other fever-causing conditions.

Panel 3: Distribution of FOU in adults by diagnostic category in eleven published series

Series	% of cases in specified diagnostic category*				
	Infection	Neoplasm	Collagen vascular disease	Miscellaneous	Undiagnosed
Ref 5; 1952-57; n=100	36	19	15	23	7
Ref 15; 1959-60; n=60	22	17	13	10	38
Ref 16; 1957-71; n=128	40	20	15	17	8
Ref 17; 1969-76; n=100	37	31	19	8	5
Ref 1; 1970-80; n=105	30	31	9	17	12
Ref 18; 1968-81; n=133	31	18	13	17	21
Ref 2; 1980-89; n=199	23	7	19	28	24
Ref 6; 1984; n=86	33	24	16	18	9
Ref 3; 1982-92; n=153	29	14	29	16	12
Ref 4; 1988-92; n=53	21	19	13	17	30
Ref 19; 1986-92; n=80	54	9	14	5	18

*Diagnostic categories differ slightly from those used in some series

Invasive procedures

Diagnosis in fewer than half the cases of FUO has resulted from excisional biopsy, needle biopsy, or laparotomy. Most FUO patients undergo at least one of these procedures, even though the yield is moderate—ie, 2·8–4·6 biopsies per final diagnosis achieved.^{1,6} The yield from biopsies in the operating-theatre or under CT guidance is greater than that of bedside biopsy procedures.⁶ The only biopsy that may often be rewarding in the absence of prior localising information is temporal artery biopsy in elderly patients with a very high erythrocyte sedimentation rate (ESR).¹¹

Exploratory laparotomy in the absence of localising features is unusual these days. Anatomical abnormalities are unlikely to have been missed by CT, leaving only diagnoses such as vasculitis, polyarteritis nodosa, granulomatous disease, or chronic cholecystitis.²⁶ Laparoscopy, including laparoscopic liver biopsy, is a less traumatic alternative. It is most helpful when other features point to abdominal disease and has had a yield of only 20% when such features are absent.³¹ Liver biopsy alone, in patients with or without recognised liver abnormalities, is less helpful than laparoscopy.³²

Approach

Attempting to diagnose the cause of FUO is a daunting task. The list of possible causes is enormous; there are no useful algorithms; and all tests that empirically have at least a modest yield should already have been done. Consequently, the clinician must rely on diligence and clinical acumen. This admonition, however bland, is relevant because newer diagnostic tests alone appear to have had little impact on the incidence or causes of FUO. Physicians should repeatedly interview and examine the patient and review laboratory test results and imaging studies, including those from other hospitals. Delay often results from the failure to recognise helpful clues in available information. Also, discontinuation as many medicines as possible and avoid procrastination when faced with the need to obtain tissue for diagnosis.

Outcome

The prognosis is determined primarily by the underlying disease and, to a lesser extent, by rapidity of diagnosis. Outcome is worst for neoplasms.¹ Diagnostic delay has contributed to death in intraabdominal infection (especially splenic abscess), miliary tuberculosis, disseminated fungal infection, and recurrent pulmonary emboli.

FUO patients who remain undiagnosed after extensive evaluation generally have a favourable outcome^{1,3,5,33} and the fever usually resolves after 4–5 weeks without sequelae. A subgroup of patients with undiagnosed FUO have clinical features which resemble polymyalgia rheumatica, vasculitis, or other inflammatory disease but do not meet accepted diagnostic criteria. These patients may have fever which responds to corticosteroid therapy.

Selected diseases

In the following sketches of selected causes of FUO the focus is on clinical features and laboratory tests likely to be of diagnostic value.

Infections

Tuberculosis The forms of tuberculosis that most often cause FUO are disseminated disease without the

characteristic miliary pattern on chest radiograph or extrapulmonary disease without clear localising features. Disseminated tuberculosis probably is the most readily treatable cause of death in patients with FUO and warrants vigorous diagnostic efforts when the disease is suspected. Serial chest radiographs may demonstrate subtle but increasing infiltrates. The ESR is usually raised and anaemia is common. A tuberculin skin test may be negative in up to one-half of patients and sputum smears may be positive for acid-fast bacilli in only one-fourth to one-half of cases. Lung and liver biopsy each demonstrate granulomas in 80–90% of cases of miliary tuberculosis; about half the granulomas will show caseation and acid-fast bacilli are seen in about half. Bone-marrow biopsy is likely to show granulomas in only half the cases, but the yield exceeds 80% when anaemia, leukopenia, and monocytosis are present. Bronchoalveolar lavage is often culture-positive but acid-fast bacilli are rare. Rapid diagnostic tests (eg, PCR) permit earlier detection of *M tuberculosis* and should be helpful in selected cases of FUO. The most important measure is to obtain additional specimens for histopathological and bacteriological examination if the initial ones are negative but tuberculosis is still suspected.

Intraabdominal abscess The diverse sites of intraabdominal abscess give rise to different clinical features. Localising symptoms, such as abdominal pain, nausea, vomiting, or diarrhoea, are common in liver or intraperitoneal abscesses or chronic cholecystitis. Tenderness on examination is reported in most cases of liver, splenic, or intraperitoneal abscess. Elderly patients typically have a more subacute course with few signs and symptoms and a long illness. Certain antecedent conditions predispose to specific intraabdominal abscesses—eg, Crohn's disease to intraperitoneal or retroperitoneal abscess and infective endocarditis, biliary tract disease, and pancreatitis to abscess of the spleen, liver, and pancreas, respectively.

Culture-negative endocarditis This has diminished in importance as culture techniques have improved but when it is suspected as the cause of FUO the laboratory should be consulted about attempts to isolate unusual pathogens by prolonged incubation (eg, two weeks rather than five days), periodic staining of blood cultures with acridine-orange, or blind subculture onto solid media. Examples are by subculture onto blood agar and into endothelial cell culture for *Bartonella* spp and onto buffered charcoal-yeast extract agar for *Legionella* spp. *Coxiella burnetii* is not recovered from routine blood cultures, and serological testing is necessary. Even with more typical endocarditis pathogens, antibiotics may temporarily interfere with culture. Without a new regurgitant murmur or evidence of peripheral emboli, the diagnosis may be obscure. Transoesophageal echocardiography is positive in over 90% of cases.

Cytomegalovirus One in four immunocompetent adults with cytomegalovirus (CMV) mononucleosis has fever lasting more than 3 weeks. The clinical presentation often resembles mononucleosis but sore throat, pharyngeal erythema, adenopathy, and splenomegaly are each present in fewer than half the CMV cases. EBV and HIV can cause a similarly protracted mononucleosis-like syndrome but prolonged fever is suggestive of CMV. Every patient with CMV should have reactive lymphocytosis and

moderately increased serum transaminase at some point. The diagnosis can be confirmed by serological testing (CMV-IgM) or viral isolation from blood.

Neoplasms

Lymphoma Fever is seen most often in advanced lymphoma and with more aggressive histological patterns of lymphoma. Constitutional, or B symptoms (fever, night sweats and weight loss), are present in a minority of lymphoma patients but on occasion dominate the clinical presentation. Lymphadenopathy, splenomegaly, unexplained anaemia or thrombocytopenia, and a very high serum lactate dehydrogenase may provide clues. Careful physical examination, a CT of chest, abdomen, and pelvis, and bone marrow examination will usually identify the sites of involvement. Biopsy may then confirm the diagnosis.

Renal-cell carcinoma Renal cell carcinoma, or hypernephroma, commonly causes fatigue and weight loss, but intermittent fever may be the presenting symptom in up to 15% of patients. The diagnosis may be suggested by microscopic haematuria or erythrocytosis linked to increased production of erythropoietin. Abnormal liver-function tests are sometimes found in patients without demonstrable liver metastases and often resolve after removal of the primary tumour.

Atrial myxoma Manifestations include fever, syncope, congestive heart failure, peripheral or pulmonary emboli, weight loss, myalgias, arthralgias, and rash. Cardiac murmur may be absent, intermittent, or positional; a low-pitched "tumour plop" is sometimes heard during diastole. A raised ESR and anaemia are common. The diagnosis is almost always established by echocardiograph y.

Collagen vascular diseases

Juvenile rheumatoid arthritis (Still's disease) The diagnosis is based entirely on clinical features, including fever, arthralgias, myalgias, arthritis, sore throat, diffuse lymphadenopathy, splenomegaly, pleuritis, and pericarditis. Fever may precede other features by a year. Fever usually is high and may spike daily or twice-daily. An evanescent macular rash sometimes becomes evident, primarily on the trunk, during fever. Illness may be continuous or episodic, with attacks separated by weeks or years. Anaemia, leukocytosis, and a raised ESR are usual, and liver enzymes are sometimes elevated. In active disease, serum ferritin levels are very high. Biopsy of lymph nodes shows reactive hyperplasia and biopsy of skin lesions shows perivascular infiltration by chronic inflammatory cells. The triad of high fever, evanescent rash, and arthritis or arthralgia in a young adult strongly suggests Still's disease, especially if sore throat is also reported.

Temporal arteritis Temporal arteritis (or giant-cell arteritis) is very rare under age 55 but accounts for about 15% of FUO in the elderly. The disease classically presents with headache, fever, anaemia, and a very high ESR. Other symptoms include fatigue, anorexia, weight loss, sweats, arthralgias, and depression, and patients may complain of scalp pain, jaw claudication, or visual disturbances. The temporal artery is tender, thickened, or nodular on examination in a minority of patients. Temporal artery biopsy is required to confirm the diagnosis. Polymyalgia rheumatica is closely associated with temporal arteritis and is characterised by pain and stiffness in the muscles of the neck, shoulders, lower back,

hips, and thighs. A dramatic response to glucocorticoid therapy can confirm the diagnosis. In an elderly patient with unexplained fever, systemic symptoms, and a very high ESR, temporal biopsy should be considered even if there are no specific signs of arteritis.

Polyarteritis nodosa The clinical manifestations vary. Malaise, myalgias, and fever are usually present and specific features reflect involvement of the arteries in organs such as the kidneys and gastrointestinal tract. Features that are highly specific include mononeuritis, testicular tenderness, and livedo reticularis. The patient will often have antineutrophil cytoplasmic antibodies and raised white-blood-cell count and ESR; hepatitis B surface antigen has been detected in at least 15% of patients. Diagnosis can be made by biopsy or by arteriography to demonstrate aneurysms or narrowing of arteries.

Miscellaneous

Sarcoidosis This systemic disease most commonly affects the lungs, skin, eyes, and lymph nodes. There is no diagnostic blood test; angiotensin-converting enzyme activity is raised in about two-thirds of patients but false-positive and false-negative results are common. The chest radiograph will almost always show bilateral hilar adenopathy and/or diffuse parenchymal infiltrates. Biopsy evidence of a mononuclear cell, granulomatous inflammatory process establishes the diagnosis.

Haematoma Uninfected haematoma can elicit a fever-producing inflammatory response. Most haematomas associated with FUO have been intraabdominal or retroperitoneal and can be visualised by CT. A notable exception is arterial wall haematoma associated with aortic dissection, where the abrupt onset of chest, back, or abdominal pain precedes the fever and anaemia.

Subacute thyroiditis The typical features of subacute thyroiditis are thyroid pain and tenderness, accompanied by malaise, myalgia, and fever. The onset is usually sudden, and about half the cases are preceded by an upper respiratory infection. Pain may be sensed in the throat rather than the neck and may radiate to the ears or jaw. Some degree of thyroid enlargement and tenderness is almost always present. Relapses may prolong the course of illness to many months. Diagnosis of subacute thyroiditis is most difficult when thyroid pain and tenderness are minimal.

Factitious fever Factitious fever and self-induced infection should be suspected when the clinical syndrome does not correspond to a known disease. Clinical clues include high temperatures without tachycardia or skin warmth, unusual fever patterns (eg, very brief spikes or loss of evening peak), and absence of fever when an observer is present. Deception by thermometer manipulation and thermometer switching is less common where mercury bulb thermometers have been replaced by rapid electronic thermometers. A remaining mechanism is surreptitious ingestion of fever-causing drugs. True infections have been self-induced by injection of body fluids or other contaminated materials. The resulting illnesses are characterised by unexplained polymicrobial bacteraemia, serial episodes of bacteraemia by different pathogens, or recurrent soft-tissue infections (cellulitis or subcutaneous abscesses). Patients with factitious fever or self-induced infection are more likely to be female and often have a medical, nursing, or paramedical background.

Familial Mediterranean fever This illness is characterised by periodic attacks of fever and abdominal pain, sometimes accompanied by pleuritic chest pain, joint pain, or painful skin lesions on the legs. In rare instances, there may be episodes of fever alone or bouts of abdominal pain without fever. Attacks usually begin before adolescence. Each episode lasts only a few days but may continue for more than a week, with intervals between attacks of several weeks. Laboratory abnormalities during attacks are leukocytosis and raised ESR and acute-phase reactants. Familial Mediterranean fever appears to be transmitted as an autosomal recessive trait and occurs primarily, but not exclusively, in ethnic groups of Middle-Eastern origin. Diagnosis may be difficult in patients who lack the typical

family history or ethnic origin, or when peritoneal signs are absent.

Drug fever The clinical characteristics of drug fever are not distinctive. Fever patterns are diverse, shaking chills occur in about half the cases, and rash or eosinophilia are infrequent. Commonly, several weeks elapse between initiation of the drug and onset of fever. Once the causative drug is stopped, fever almost always resolves within two days. The list of implicated agents is lengthy and includes some drugs given to treat fever (eg, aspirin, nonsteroidal antiinflammatory drugs, and antibiotics). Diagnosis may be especially difficult when infection prompted administration of the drug—eg, isoniazid for tuberculosis or vancomycin for suspected bacteraemia.

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