STATE-OF-THE-ART CLINICAL ARTICLE

Fever of Unknown Origin in Adults

J. V. Hirschmann

From the Seattle Veterans Affairs Medical Center, Seattle, Washington

In 1907 Richard C. Cabot, a physician at the Massachusetts General Hospital (Boston) and founder of its clinicopathological conferences, published a paper entitled "The Three Long-Continued Fevers of New England" [1]. Reviewing hospital records, autopsies, and cases from private practice, he found 784 patients with >2 weeks of continuous temperatures above 99°F and reported that 91% suffered from one of three disorders—typhoid fever (75%), tuberculosis (7%), and "sepsis" (i.e., pyogenic bacterial infections such as abscesses and endocarditis) (9%). Most of the remaining cases were due to other infectious diseases, including meningitis, influenza, syphilis, and gonorrhea. Through the 1950s, clinicians in the United States and western Europe continued to describe patients with lengthy or unexplained fevers, but these series were retrospective, had differing or undefined criteria for fever, involved various intensities of evaluation, and typically failed to identify the etiology in most cases. Among those with prolonged fever for whom a specific diagnosis emerged, the most common causes continued to be a wide variety of infections, including syphilis, brucellosis, endocarditis, and, especially, tuberculosis.

Believing that most patients with protracted, perplexing fever had *non-infectious* diseases, Paul B. Beeson conducted a prospective study from 1952 to 1957 at Yale University, and, with Robert G. Petersdorf, published this experience with 100 patients in 1961 [2]. The intent of this series was to study genuinely perplexing cases of prolonged fever: those included in it had to satisfy three prerequisites that have since formed the definition of fever of unknown (or undetermined) origin (FUO): (1) illness of >3 weeks' duration; (2) fever higher than 101°F (38.3°C) on several occasions; (3) an uncertain diagnosis despite 1 week of study in a hospital. The purpose of these criteria was to exclude from consideration acute, self-limited illnesses, healthy people whose temperatures slightly exceeded the normal range (those with "habitual hyperthermia"), and disorders readily identifiable after a brief evaluation. Since hospitalization is often unnecessary, Petersdorf has suggested revising the third criterion to: no diagnosis established despite 1 week of intensive evaluation [3].

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Reprints or correspondence: Dr. J. V. Hirschmann, Medicine Service (111), Seattle VA Medical Center, 1660 South Columbian Way, Seattle, Washington 98108.

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Causes

In the series that Petersdorf and Beeson reported from the 1950s, the etiologies of FUO were infections (36% of cases), neoplasms (19%), rheumatologic diseases (15%), miscellaneous (23%), and undiagnosed (7%). Despite the passage of four decades, changes in diagnostic procedures, and differences in the individual disorders identified, the distribution of causes has remained remarkably constant in most reports from the 1960s to the 1990s: infections, 30%–40%; neoplasms, 20%–30%; rheumatologic diseases, 10%–20%; miscellaneous, 15%–20%; and undiagnosed, 5%–15%. Infections are generally more common—40%–60%—in tropical and subtropical countries, however, than in those with temperate climates, such as the United States, western Europe, and Japan. More than 200 diseases can cause FUO; the major diagnostic considerations appear in table 1. Among this impressive array of disorders, too numerous to permit individual discussion, certain conditions warrant comment because of their frequency, distinctive features, or unfamiliarity to many clinicians.

Infections. Infections that cause FUO may be localized or systemic. A major difficulty in diagnosing focal infections is that symptoms and signs incriminating the affected area are commonly absent, inconspicuous, or unimpressive. Infective endocarditis provides an example of how several problems can obscure the diagnosis of a focal infection: murmurs may be undetectable or unchanged from previous examinations, and other physical findings, such as Osler's nodes and Janeway's lesions, are rare. Furthermore, microbiological confirmation is sometimes problematic. For example, diagnostic delay may occur because of slow growth of the pathogen in blood cultures, which, even with contemporary microbiological techniques, can require >1 week for detecting bacteria such as the HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella* species).

On the other hand, blood cultures may remain negative, most commonly because of previous antimicrobial therapy, which can render specimens sterile for days to weeks, even after treatment has ended. Another cause of culture-negative endocarditis is infection with microbes, such as *Chlamydia* species, *Coxiella burnetii,* or *Bartonella* species, that fail to grow in routine media and that require special microbiological procedures (e.g., different culture methods or serologic tests) to detect.

Echocardiography can help diagnose endocarditis—in demonstrating vegetations, the sensitivity of the transthoracic ap-

Table 1. Major causes of fever of unknown origin.

- Infections
  - Localized
    - Endocarditis
    - Intraabdominal infections
    - Urinary tract infections
    - Osteomyelitis
    - Upper respiratory tract infections
    - Infected peripheral vessels
  - Generalized
    - Bacterial
    - Mycobacterial
    - Fungal
    - Viral
    - Parasitic
- Neoplasia
  - Lymphoproliferative disorders
  - Leukemia
  - Myelodysplastic diseases
  - Solid tumors
- Rheumatologic disorders
  - Adult Still's disease
  - Giant cell arteritis, polymyalgia rheumatica
  - Other forms of vasculitis (e.g., polyarteritis nodosa, Wegener's granulomatosis, Takayasu's arteritis)
  - Other rheumatologic disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, Sjogren's disease)
- Miscellaneous
  - Granulomatous disorders
  - Alcoholic hepatitis
  - Vascular disorders
    - Pulmonary emboli
    - Hematoma
  - Drug fever
  - Hereditary (e.g., familial Mediterranean fever)
  - Endocrine
    - Hyperthyroidism
    - Thyroiditis
    - Adrenocortical insufficiency
  - Factitious fever

proach is ~75%, that of the transesophageal is ~90%. False-negative results occur because the technique can miss very small vegetations; larger ones may have embolized, leaving no trace; valve infection can exist without vegetations; or infection may form on the mural endocardium rather than on the valves. False-positive results can occur because abnormalities from previous, healed endocarditis persist or because thickening or other anomalies of the valve leaflet resemble vegetations. The non-infectious fibrin-platelet thrombi that develop in either systemic lupus erythematosus (Libman-Sacks endocarditis) or chronic diseases such as cancer (nonbacterial thrombotic or marantic endocarditis) are sometimes large enough to be visible on an echocardiogram and are especially confusing since the underlying disorders can further mimic infective endocarditis in causing fever.

Another common etiology of focal infections in FUO has been intraabdominal suppuration, including hepatic, diverticular, splenic, subphrenic, pancreatic, biliary tract, psoas muscle, and pelvic infections. Many patients have predisposing conditions that should suggest these diagnoses. Hepatic abscesses usually arise from infections elsewhere, the organisms reaching the liver via the biliary tract or by hematogenous spread through the systemic or portal circulations. Important information that might indicate liver abscesses as the cause of fever, therefore, includes previous or concurrent gallbladder or bile duct diseases, especially obstruction; intraabdominal infections such as diverticulitis or appendicitis; hepatic trauma, which may produce a hematoma that later becomes infected; prior systemic bacteremia; and travel to areas where amebiasis is endemic.

Splenic abscesses tend to occur in patients with preceding or simultaneous infection elsewhere (often from illicit intravenous drug use) that spreads contiguously or hematogenously to the spleen. These infections also develop in those with impaired systemic host defenses due to chemotherapy or immunodeficiency (in whom fungi are common pathogens), and in those with splenic abnormalities caused by trauma or hematologic disorders such as sickle-cell and other hemolytic anemias. Subphrenic abscesses are usually a complication of previous abdominal surgery, especially operations involving the stomach, duodenum, biliary tract, or spleen, but some may occur from preceding perforation of abdominal viscera. Pancreatic abscesses most commonly appear a few weeks after an attack of acute pancreatitis. FUO has occurred from biliary tract suppuration in patients with cholecystitis; with cholangitis, which can cause recurrent episodes of pyrexia (''Charcot's intermittent fever'') due to periodic bile duct obstruction; and with empyema of the gallbladder, most often associated with cholelithiasis. In addition, FUO has arisen from psoas muscle abscesses, which may develop following gastrointestinal tract perforations, including those from Crohn's disease; as a complication of spinal osteomyelitis; or as an apparently primary process, presumably through hematogenous spread from a transient bacteremia or an occult infection.

Pelvic abscesses typically occur as a complication of colonic diverticulitis, appendicitis, pelvic inflammatory disease, or intraabdominal surgery. Because inflammation may extend to involve the rectum or urinary tract, diarrhea and tenesmus or urinary frequency, dysuria, and urgency may be prominent, potentially misleading symptoms. Contemporary imaging techniques, such as abdominal ultrasonography and CT, which can readily detect these infections, even early after onset, have made intraabdominal sepsis a less common cause of FUO than in the past.

Another frequent site of infection is the urinary tract. Pyelonephritis may produce a protracted fever, even in patients receiving antimicrobial therapy active against the responsible pathogens, when it is complicated by a perinephric abscess, urinary tract obstruction, or intrarenal suppuration, such as focal pyelonephritis (focal bacterial nephritis) and intrarenal abscess. Urine cultures can be negative before treatment when obstruction is present, since infected urine may not reach the bladder, or when peri-

nephric abscess occurs, since this infection lies outside the renal capsule and often does not communicate with the collecting system. Clinicians should suspect perinephric abscesses in patients (frequently diabetics) with preceding urinary tract surgery, infections, obstruction, or stones. Malakoplakia and xanthogranulomatous pyelonephritis, unusual host responses to parenchymal renal infection, can also cause prolonged fever.

Patients with prostatic abscesses, who are usually >50 years of age, often have urinary frequency and difficulty initiating micturition, but these symptoms are common with uncomplicated benign prostatic hyperplasia and may not suggest an infection. Rectal examination usually discloses prostatic enlargement, but fluctuance, tenderness, or bogginess is typically absent.

The oral cavity and upper respiratory tract may also harbor infections without impressive localizing features. Periapical dental abscesses have caused several cases of FUO, sometimes manifesting as intermittent febrile episodes that may follow eating. Most patients have no dental symptoms, but some complain of painful, loose teeth or discomfort with chewing, and a large percentage have abnormalities on careful oral examination, including severe periodontal disease; discolored, dead teeth; and visible or palpable abscesses. In many cases, the diagnosis depends upon dental radiographs. Antimicrobial therapy alone rarely eradicates the fever: dental extraction is usually necessary. Otitis media and sinusitis have also produced FUO but are rare causes.

Focal infections of the bone or blood vessels are another source of FUO. Most cases of osteomyelitis have involved the vertebrae or infected joint prostheses, and, although the patients typically have local discomfort, it is often minimal and its significance unappreciated. Septic phlebitis may result from illicit intravenous drug use, indwelling catheters, and cardiac pacing wires. Arterial vessels that may become infected, leading to FUO, include native arterial aneurysms (in which the most common pathogens are *Staphylococcus aureus* and *Salmonella* species), vascular grafts, and traumatic arteriovenous fistulas.

Systemic bacterial infections that can cause FUO include salmonellosis, brucellosis, chronic meningococcemia, Whipple's disease, yersiniosis, tularemia, syphilis, disseminated gonococcal infection, Q fever, psittacosis, borreliosis, leptospirosis, cat-scratch disease, and melioidosis (in Southeast Asia). The most common systemic bacterial infection, by far, however, has been tuberculosis. Although involvement may be focal, especially in extrapulmonary sites such as the peritoneum, patients often have disseminated (miliary) disease. Two potentially useful examinations are often unhelpful: the tuberculin test is frequently negative in the miliary and peritoneal forms, and the chest radiograph is normal in ~50% of most types of extrapulmonary tuberculosis. Even with miliary disease, patients may be ill for several weeks before the characteristic small opacities (~2 mm in diameter) appear on chest films.

Fungi uncommonly cause protracted, unexplained fevers. While *Histoplasma capsulatum* and *Coccidioides immitis* can produce widespread disease in previously healthy people, many patients with these infections and most with other disseminated mycoses that have caused FUO, such as candidiasis, aspergillosis, and cryptococcosis, have seriously impaired host defenses.

The most common viral cause of FUO is cytomegalovirus infection, which commonly produces atypical lymphocytosis and elevated hepatic enzyme levels. Even healthy hosts can have prolonged fevers; ~25% of patients are febrile for >3 weeks. Fever, myalgia, and malaise are the most frequent symptoms; splenomegaly, lymph node enlargement, sore throat, and rash develop in a minority. Other agents to consider in cases of FUO are Epstein-Barr virus, which causes infectious mononucleosis, and HIV, which by itself rarely produces fever, but through its immunosuppressing effects predisposes patients to infection with other organisms.

In tropical or subtropical areas parasitic infections incriminated in FUO include malaria, amebiasis, trypanosomiasis, leishmaniasis, and fascioliasis. In temperate climates parasitic disorders to consider are toxoplasmosis, which can cause both a disease in normal hosts resembling infectious mononucleosis and disseminated infection in immunodeficient hosts; babesiosis; and *Pneumocystis carinii* infection in immunocompromised patients, especially those with HIV infection.

Neoplasia. The neoplastic disease that most commonly causes FUO is lymphoma, both Hodgkin's and non-Hodgkin's types. Patients usually have a daily temperature elevation, but a relapsing (Pel-Ebstein) fever, which disappears and reappears at intervals of several days, occasionally occurs, especially with Hodgkin's disease. Several factors may render the diagnosis of lymphoma difficult: peripheral lymph nodes may be normal on physical examination, the diseased ones being in the thoracic or abdominal cavities; mediastinal lymphadenopathy may be inapparent on plain chest films; biopsies may be nondiagnostic because of insufficient sample size; or the lymphoma, usually non-Hodgkin's, may predominantly or exclusively involve non-nodal structures, such as the liver, spleen, bone marrow, or blood vessel lumina (i.e., intravascular or angiotropic large-cell lymphoma).

Patients with hepatic lymphoma usually have right-upper-quadrant abdominal pain, hepatomegaly, and elevated liver enzymes, while patients with primary splenic involvement typically have left-upper-quadrant abdominal discomfort, weight loss, and a palpable spleen. In both disorders CT scans demonstrate single or multiple masses in the affected organ, and large biopsies may be necessary to establish the diagnosis. Patients with isolated bone marrow involvement usually have pancytopenia and elevated liver enzymes; repeated bone marrow biopsies are often required for definitive diagnosis. Intravascular lymphoma, typically characterized by fever, abnormal mentation, and skin lesions (including nodules, plaques, petechiae, and purpura), is particularly difficult to identify, and often the diagnosis is apparent only at autopsy.

The disease formerly called malignant histiocytosis, which has caused several cases of FUO, belongs among the lympho-

mas. The usual clinical features are fever, weight loss, hepatosplenomegaly, generalized lymph node enlargement, pancytopenia, and elevated liver enzymes. Examination of affected organs demonstrates infiltration by what appear to be anaplastic histiocytes and, often, hemophagocytosis by these cells or by benign-appearing cells. Contemporary pathologic techniques, however, identify most of the malignant cells as lymphoid and the disease as anaplastic large-cell lymphoma.

Other disorders that affect the lymph nodes, can cause FUO, and are neoplasms or resemble them include angioimmunoblastic lymphadenopathy, Kikuchi's necrotizing lymphadenitis, angiofollicular lymph node hyperplasia (Castleman's disease), and inflammatory pseudotumor. Angioimmunoblastic lymphadenopathy with dysproteinemia typically occurs in the sixth and seventh decades of life and causes lymph node enlargement that is usually diffuse, and, in most patients, hepatosplenomegaly. Pruritus and a nonspecific, generalized, erythematous eruption with macules and papules are common, and this disorder often seems to begin as a hypersensitivity reaction to some medication. Laboratory abnormalities present in most cases include anemia (usually associated with a positive Coombs' test) and polyclonal hypergammaglobulinemia. Eosinophilia occurs in ~30% of cases.

Patients with Kikuchi's necrotizing lymphadenitis are usually women <40 years of age who have enlarged cervical lymph nodes and, often, fever, but no additional constitutional symptoms. Other lymph node sites, including intrathoracic and intraabdominal ones, may be involved. Neutropenia is common, and liver tests are occasionally abnormal. In most cases, the disorder resolves spontaneously in 1 to 4 months.

Castleman's disease can be localized or multicentric. Localized disease, which usually occurs in patients <30 years of age, consists of enlarged lymph nodes, predominantly in the abdomen or mediastinum. In 90% of those with the localized form, histologic examination of the lymph nodes reveals the hyaline-vascular variety, and patients have no systemic symptoms. In contrast, the plasma-cell type usually causes constitutional complaints, including fever, weight loss, and, occasionally, peripheral neuropathy, as well as laboratory abnormalities of anemia, hypergammaglobulinemia, and renal dysfunction. Following excision of the involved lymph nodes, the disorder typically resolves without recurrence.

Multicentric Castleman's disease occurs in older patients (mean age, 56 years), primarily involves the peripheral lymph nodes, and commonly causes fever (either persistent or episodic), hepatosplenomegaly, and anemia. The diagnosis may be difficult, sometimes requiring repeated biopsies, and depends on characteristic, but unfortunately nonspecific, histologic findings; clinical evidence of multisystem involvement; disease in several lymph nodes; and exclusion of other disorders, such as HIV infection and lymphoma, that cause similar pathologic alterations.

Inflammatory pseudotumor of the lymph nodes may affect either peripheral or deep sites such as the retroperitoneal or mediastinal nodes. Persistent or episodic fever is common, hypergammaglobulinemia and anemia are occasional, but hepatosplenomegaly is rare. The cause of this disease is unknown, and it often resolves spontaneously, although surgical excision of affected tissue may be curative.

In cases of FUO due to leukemia (most commonly the acute non-lymphocytic types), the peripheral blood smear reveals no definitive findings (aleukemic leukemia), and establishing the diagnosis requires bone marrow examination. This procedure is also necessary for detecting the myelodysplastic syndromes, which comprise several hematologic disorders that typically occur in patients >50 years of age and consist of abnormal proliferation and differentiation of the hematopoietic stem cell. Nearly all patients with myelodysplasis have anemia, sometimes accompanied by thrombocytopenia, leukopenia, or both; occasionally, fever is the major constitutional feature. Diagnostic clues detectable on the peripheral blood smear include the erythrocyte abnormalities of macrocytosis, anisocytosis, poikilocytosis, nucleated red cells, and acanthocytosis; hypogranulation and hyposegmentation of the neutrophils (Pelger-Huet-like anomaly); and hypogranularity or hypergranularity and enlargement of the platelets.

The solid tumor that most frequently causes FUO is renal cell carcinoma; fever occurs in ~20% of cases and is the presenting symptom in ~15%. Some patients have unexplained elevations of hepatic transaminases and alkaline phosphatase and a prolonged prothrombin time, findings that erroneously suggest a primary liver disorder. Many other neoplasms can cause FUO, including carcinomas originating in the lung, breast, ovary, stomach, esophagus, colon, gallbladder, and pancreas; nasopharyngeal carcinoma; intestinal leiomyosarcomas; sarcomas of other sites; and primary hepatic tumors (either benign or malignant). Patients with cancer, however, do not seem to have fever more commonly when liver metastases are present than when they are absent.

Another important neoplasm to consider as a cause of FUO is atrial myxoma; fever is present in ~30% of patients with this cardiac tumor. Other clinical findings include constitutional symptoms such as myalgias, arthralgias, weight loss, and fatigue; embolic phenomena (in ~30–40% of patients); hypergammaglobulinemia; and anemia, which is usually hypoproliferative, but can occasionally be hemolytic because of mechanical destruction of RBCs by the tumor. Diastolic murmurs, often position-dependent, are audible shortly after the second heart sound (''tumor plop'') in about one-third of patients.

Rheumatologic disorders. In recent series the most common rheumatologic disorder causing FUO has been adult Still's disease. The diagnosis is strictly a clinical one, since no definitive laboratory test exists. The onset of this disease characteristically occurs between 16 and 35 years of age, and the typical clinical features are fever, which usually exceeds 39.5°C (103.1°F) and can reach 42°C (107.6°F); myalgias; arthralgias; arthritis; and leukocytosis. Other findings may include sore

throat, lymph node enlargement, splenomegaly, and an evanescent, salmon-colored exanthem, which often appears with the febrile episodes.

Two disorders seen almost exclusively in patients >50 years of age are giant cell arteritis, in which pyrexia and malaise may be the only manifestations, and polymyalgia rheumatica, which can cause fever, arthralgias, and myalgias. The erythrocyte sedimentation rate (ESR) is nearly always >40 mm/h in patients with either of these related diseases. In many patients with FUO due to giant-cell arteritis, careful questioning will elicit classic symptoms of this disease such as headache, jaw claudication, or visual loss, and many have muscle complaints characteristic of polymyalgia rheumatica—symmetrical pain and stiffness that are typically worse in the morning and affect the lumbar spine and large proximal muscles, such as those of the neck, shoulders, hips, and thighs. Physical examination often reveals scalp tenderness or a palpably abnormal temporal artery. About 25% of patients with giant cell arteritis have elevated liver enzymes, predominantly alkaline phosphatase, but sometimes transaminases, falsely suggesting a primary liver disorder. The diagnosis of polymyalgia rheumatica remains a clinical one, but in patients with giant cell arteritis an extensive biopsy of a temporal artery (whether abnormal on physical examination or not) usually yields a definitive diagnosis.

Other vasculitides that cause FUO include Wegener's granulomatosis, Takayasu's arteritis, cryoglobulinemia, and, especially, polyarteritis nodosa. Clues to the diagnosis of polyarteritis nodosa include mononeuritis multiplex (present in ~60% of cases), myalgias with muscle tenderness, skin lesions (typically palpable purpura and livedo reticularis), intense abdominal pain (primarily due to ischemia of the small intestine), renal impairment, and orchitis. Definitive diagnosis requires biopsy of affected tissue.

Miscellaneous causes. Some forms of apparently non-infectious granulomatous inflammation can cause FUO. The clinical features may conform to a recognizable pattern of illness such as Crohn's disease or sarcoidosis. The findings characteristic of these disorders, however, are frequently absent, despite the existence of non-caseating granulomas in several tissues, including lymph nodes, bone marrow, kidney, spleen, and, especially, the liver (granulomatous hepatitis). Patients with this kind of idiopathic granulomatosis typically have fever, sweats, malaise, arthralgias, myalgias, and weight loss. Levels of liver enzymes, primarily alkaline phosphatase, are increased in ~60% of cases. Diagnosing this disorder requires a biopsy of involved tissue and exclusion of other conditions that produce this histologic pattern, such as tuberculosis, certain disseminated fungal infections, and lymphoma. Nearly all patients with idiopathic granulomatosis respond to systemic corticosteroid therapy.

Alcoholic hepatitis, often unsuspected because patients deny or minimize their ethanol intake, has been a frequent cause of FUO in some series. A helpful feature is that the aspartate aminotransferase level almost always exceeds that of alanine aminotransferase (usually by a ratio of >2:1), is rarely >600 U/L, and is frequently only mildly increased. Leukocytosis, often to high levels, may also occur.

Two important vascular causes are pulmonary emboli and hematomas in enclosed spaces. About one-half of patients with pulmonary emboli are febrile. The fever, which characteristically is less than 39°C (102.2°F), but may exceed 40° (104°F), commonly resolves a few days following therapy. It can last several weeks, however, usually when the emboli are recurrent, undetected, and, therefore, untreated. In patients with FUO due to pulmonary emboli, predisposing factors such as cancer or recent immobility are typically present, but pulmonary symptoms may be absent, unimpressive, or attributable to another cause, and chest radiographs commonly show no abnormalities.

Hematomas causing FUO usually arise from hemorrhages into the abdominal cavity or retroperitoneal space, but may also occur from bleeding within the wall of an aneurysm or dissection of the thoracic or abdominal aorta. In patients with aortic dissection, persistent fever and anemia typically follow an episode of chest, back, or abdominal pain that spontaneously resolves.

Drug fever can occur with virtually any medication, even one administered for long periods without previous problems. In ~20% of cases the presence of eosinophilia or a rash provides a clue to the correct diagnosis. Temperatures above 40°C (104°F), rigors, hypotension, and leukocytosis can all develop with drug fever, often making it clinically indistinguishable from other types of pyrexia, including bacterial sepsis. The pattern of fever caused by drugs is rarely distinctive; indeed, the most common is the "hectic" type, often erroneously considered pathognomonic of infection, in which there is a large difference between the acme and nadir of the daily temperature.

Several disorders seem, in many cases at least, to be hereditary causes of episodic fever and usually begin in childhood. Sometimes, however, patients have no family history, and, occasionally, the onset is during adulthood. Familial Mediterranean fever consists of recurrent fever, peritonitis, and leukocytosis and affects primarily Arabs, non-Ashkenazic Jews, and Armenians, but a similar disorder has occurred in members of other ethnic groups, such as those from northern European countries, including Ireland, where it is called familial Hibernian fever. Another disease, described mostly in the Netherlands, but also in other European countries and Japan, causes a markedly elevated serum level of polyclonal immunoglobulin D and recurrent attacks of fever, often preceded by chills and accompanied by bilateral cervical lymph node enlargement, headache, abdominal pain, arthralgias, and skin lesions, predominantly erythematous macules or papules.

The two most common endocrine diseases responsible for FUO have been hyperthyroidism and subacute thyroiditis. In both, fever may be the major clinical manifestation, often accompanied by weight loss. With subacute thyroiditis, these systemic features seem to arise from inflammation rather than thyrotoxicosis, since patients are usually euthyroid. Most have

no local neck pain, and, although diffusely enlarged, the thyroid is typically nontender. A rare, potentially fatal, but eminently treatable endocrine cause of FUO is adrenocortical insufficiency, a diagnosis to consider in patients with such accompanying features as nausea, vomiting, weight loss, skin hyperpigmentation, hypotension, hyponatremia, and hyperkalemia.

Schnitzler's syndrome, first described in 1974, is a recondite disease that begins in adulthood and consists of persistent fever, severe bone pain accompanied by radiologic evidence of hyperostosis, and chronic nonpruritic urticaria, which on a skin biopsy may demonstrate leukocytoclastic vasculitis [4]. Other common clinical findings are lymph node enlargement and hepatomegaly. All patients have a monoclonal IgM gammopathy, but no evidence of Waldenstrom's macroglobulinemia, and most have elevated ESRs without hypocomplementemia or cryoglobulinemia.

Factitious fever, a bizarre disorder included in virtually all series of FUO, characteristically occurs in young women, often paramedical personnel. They may manipulate thermometers, an uncommon practice now that rapid electronic devices have widely replaced mercury instruments, or induce fever by such maneuvers as injecting themselves with microbes or other pyrogens. One clue suggesting the diagnosis is the patients' healthy appearance, an especially impressive finding since many provide long, often dramatic, narratives of numerous serious illnesses. Some also fabricate or exaggerate other elements in their history, such as educational or professional accomplishments. Frequently, their fever lacks the normal diurnal pattern, rapid defervescence occurs without the expected diaphoresis, the height of the temperature is extreme—>41.0° (105.8°F)—and the pyrexia is unaccompanied by tachycardia. In some, physical examination reveals evidence of self-mutilation, injection of foreign material, or other factitious disease.

Diagnosis

By definition, FUO is a diagnostic challenge, but rarely is the source of difficulty the presence of an obscure disease unfamiliar to clinicians. Insufficient information is available to provide a statistical likelihood for individual diagnoses in patients with FUO or even to rank the disorders reliably in terms of their frequency, but a review of the series of patients studied since 1980 provides a rough indication of the most common current causes [5–12]. About half of patients for whom a diagnosis emerged had one of the following seven conditions: tuberculosis, endocarditis, lymphoma, solid tumors, adult Still's disease, vasculitis, and familiar rheumatologic ailments (e.g., systemic lupus erythematosus, Sjogren's disease). The remaining causes were mostly a scattering of well-known clinical entities such as intraabdominal abscesses, urinary tract infections, drug fever, inflammatory bowel disease, and pulmonary emboli. The major difficulty in establishing the diagnosis, therefore, is not that the diseases involved are rare but rather that the characteristic features that render these disorders clinically recognizable are absent or subtle. Typically, however, some clue is present from the history, physical examination, or initial laboratory and imaging studies that can help direct the diagnostic approach.

Many patients with FUO can undergo appropriate investigation primarily or exclusively as outpatients. A careful history, thorough physical examination, and thoughtful assessment of the initial laboratory and radiographic studies are the core of a discerning diagnostic approach. Especially important in the history is information about previous medical problems and surgical procedures, travel, exposure to animals and to tuberculosis, and prior tuberculin skin tests. A patient's age is not usually relevant in the differential diagnosis, except that adult Still's disease, factitious fever, and infections due to cytomegalovirus and Epstein-Barr virus are rare in the elderly, while polymyalgia rheumatica and giant cell arteritis are virtually confined to that age group.

Assessment of the fever. One of the first steps in evaluating a patient with an FUO is to ensure that a genuine fever is present. Of 347 patients admitted to the National Institutes of Health (NIH; Bethesda, MD) for prolonged fever, 35% either had no fever or had a factitious one [13]. After confirmation of bona fide pyrexia, however, an examination of neither its height nor its pattern (such as remittent or intermittent) is helpful in suggesting a specific diagnosis. Similarly, although episodic FUO (defined as a fluctuating fever with apyrexial intervals of >2 weeks) is less commonly due to infection than FUO with continuous fever, the differential diagnosis of this form is substantial and diverse, including, for example, adult Still's disease, colonic carcinoma, Crohn's disease, inflammatory pseudotumor of the lymph nodes, and drug fever. Other features unhelpful in discriminating among the numerous sources of FUO are the presence of shaking chills, which may be present in many infectious and non-infectious disorders; night sweats; and relative bradycardia (a heart rate lower than expected for the degree of fever), which may occur not only with various infections, but also with neoplasms, rheumatologic conditions, and other diseases.

A fever's duration may be somewhat useful—those persisting for very protracted periods are less likely to be from infections or neoplasms than from other causes—but many exceptions exist. The NIH series, for example, included cases of osteomyelitis, subphrenic abscess, malaria, trypanosomiasis, and Whipple's disease that caused fevers for >1 year. A patient with lymphoma was febrile for >2 years, and two with colonic carcinomas had fevers for 1.5 and 3 years [13].

Physical examination. Several sites that clinicians often assess perfunctorily, if at all, require especially careful scrutiny. Examination of the eyes should include the conjunctiva (to detect petechiae that may occur with endocarditis and lymphoid hyperplasia that occasionally develops in lymphoma), the sclera (to discover scleritis, seen in several rheumatologic disorders), and the anterior structures (to detect uveitis). The examiner should dilate the pupil to allow thorough examination of the

fundus. Retinal abnormalities associated with infections include Roth's spots (white-centered hemorrhages) with infective endocarditis, yellowish-white choroidal lesions with tuberculosis and certain disseminated fungal infections (i.e., blastomycosis, coccidioidomycosis, candidiasis, and cryptococcosis), and active retinitis caused by disseminated toxoplasmosis or cytomegalovirus in immunocompromised patients, especially with HIV infection. Patients with malignancies may have choroidal metastases, usually from a breast or lung primary. Leukemia can cause intraretinal hemorrhages, Roth's spots, and leukemic infiltrates. Various forms of vasculitis produce cotton-wool exudates, intraretinal hemorrhages, and vascular occlusive disease, while sarcoidosis can cause perivascular sheathing ("candle-wax drippings") and choroidal nodules.

Clinicians should carefully examine the lymph nodes, especially in the cervical area, the most common site for lymphomas, infectious mononucleosis, and Kikuchi's necrotizing lymphadenitis. The examiner should peruse the entire skin surface and oral mucous membranes. The simple procedure of a punch biopsy of abnormal or suspicious lesions may yield a definitive diagnosis or reveal changes (e.g., leukocytoclastic vasculitis) that help direct further diagnostic tests. In infective endocarditis, findings on examination of these areas include red or purplish, painful nodules sometimes with a whitish center (Osler's nodes) on the pads of the fingers and toes; non-tender red macules (Janeway's lesions) on the palms and soles; splinter hemorrhages in the nailbeds; and petechiae on the palate.

In salmonellosis, rose spots (blanching pink papules 2–3 mm in diameter) may appear on the trunk, become brown, and fade within 3–4 days. In chronic meningococcemia rashes develop when the temperature rises and consist of macules, papules, and nodules that appear on the trunk and extremities, but nearly always spare the palms and soles. Petechiae are uncommon. In disseminated gonococcal disease the skin lesions are usually red macules or petechiae that evolve into vesicles and pustules on a erythematous or hemorrhagic base. They are characteristically sparse, painful, and restricted to the distal extremities.

Diffuse cutaneous hyperpigmentation may occur in Whipple's disease. The skin lesions present in disseminated fungal infections include papules and nodules progressing to crusted, verrucous growths in blastomycosis, warty nodules and subcutaneous abscesses that may drain in coccidioidomycosis, and erythematous papules, pustules, subcutaneous nodules, or cellulitis in cryptococcosis. In HIV-infected patients the cryptococcal lesions are often skin-colored nodules with a central depression, resembling molluscum contagiosum. Oral ulcers are frequent in disseminated histoplasmosis.

Cutaneous metastases typically occur in the vicinity of the primary (e.g., the chest wall for lung and breast cancers, the abdomen for those originating in the bowel, ovary, and bladder) and often in sites of previous biopsy, cancer surgery, or radiation. They are usually subcutaneous or cutaneous, moveable, firm (sometimes rock-hard), and painless nodules. They are commonly skin-colored, but occasionally red, purple, or brown, and tend to appear in clusters. Two areas to examine carefully are the umbilicus, where metastases from intraabdominal primaries (Sister Mary Joseph's nodules) develop, and the scalp, the site of ~5% of all metastases, especially from the lung, kidney, and breast. Cutaneous manifestations of lymphomas, primarily non-Hodgkin's, include purplish papules, nodules, and plaques that are usually multiple and have a predilection for the scalp, face, and neck.

Leukemia in the skin (leukemia cutis) can cause macules, papules, nodules, plaques, ecchymoses, palpable purpura, and ulcers. Sweet's syndrome, which may occur either as an idiopathic disease, sometimes producing FUO, or as a disorder associated with hematologic or solid tumors, causes fever, leukocytosis, and multiple, erythematous, painful plaques that can have small bumps, pustules, and vesicles on their surface.

The most common dermatologic finding in patients with rheumatologic diseases causing FUO is cutaneous vasculitis, which typically produces palpable purpura on the lower extremities and other areas of dependency, such as the buttocks in patients who remain recumbent for prolonged periods. Other manifestations are urticaria, ulcers, infarcts, nodules, and livedo reticularis, a purplish discoloration in a net-like pattern. Oral ulcers occur in systemic lupus erythematosis and Behçet's syndrome.

Laboratory and imaging tests. The initial laboratory evaluation for most patients with FUO should include a complete blood count with differential, urinalysis and urine culture, serum electrolytes, renal and hepatic tests, and blood cultures, which may be positive in many focal and systemic infections. Obtaining more than three blood cultures from separate venipunctures over a 24-hour period, however, is generally unrewarding, except in suspected prosthetic valve endocarditis, in which negative specimens are more common than in infections on native valves, and in patients with recent systemic antimicrobial therapy, for whom cultures of blood taken at intervals of several days are more appropriate than diurnal samples.

Patients should have a chest radiograph, which is valuable not only for disclosing intrathoracic disorders but also for suggesting intraabdominal pathology. In most patients with subphrenic, splenic, hepatic, and pancreatic abscesses, an ipsilateral finding of atelectasis, an elevated hemidiaphragm, or a pleural effusion is present, and in a few cases an intraabdominal mass is visible on the subdiaphragmatic portion of the film. Because the initial chest radiograph may be unrevealing in miliary tuberculosis, a chest CT scan or repeated radiographs every week or so are reasonable tests in suspected cases.

Unless another diagnosis is probable, clinicians should consider drug fever early in the course of the evaluation and withdraw all medications that the patient was receiving when the fever began, including non-prescription drugs and nutritional supplements. The length of time of previous use is irrelevant since medications that a patient has consumed without problems for years can cause fever. Drug fever will almost always

abate within 48–72 hours after cessation of the responsible agent, irrespective of the kind of medicine or the duration of its administration. During this brief diagnostic period of medication withdrawal, patients can receive unrelated alternatives in place of drugs that are considered essential to continue. Persistence of fever beyond 72 hours after stopping a medicine generally exonerates the drug as a cause. If the fever remits, the clinician can definitively confirm the diagnosis by reinstituting the agent, which characteristically elicits fever again within a few hours. This procedure is safe unless organ damage, such as interstitial nephritis or hepatitis, has occurred.

In designing a diagnostic approach the practitioner should especially consider sites of previous surgery, not only those related to recent procedures but also those involving implanted prosthetic devices, since infection acquired at the time of their insertion may remain clinically inapparent for months to years. Moreover, such foreign bodies may become infected via a hematogenous route or through local spread from an occult source. Petersdorf's Law enunciates this concern: "When the diagnosis is obscure, look at the surgical scar for sure" [14].

Despite the availability of a panoply of blood tests and imaging techniques, many patients still require invasive procedures to obtain material that will yield a definitive diagnosis from culture or histologic examination. Abdominal CT scanning, for example, constitutes a major advance in detecting intraabdominal pathology and is a rewarding early investigation for patients with symptoms or signs of abdominal disorders or those with no indication of disease elsewhere. This examination, however, rarely establishes a definitive diagnosis; instead, one of its primary contributions is to identify abnormal tissue, thereby indicating the site where invasive procedures such as percutaneous needle biopsy, aspiration, or catheter placement are likely to be worthwhile. These CT-guided tests frequently disclose the fever's cause, but laparoscopy or laparotomy may still be necessary when the sample obtained is insufficient or nondiagnostic.

In the past many patients with FUO—even without evidence of intraabdominal disease—underwent exploratory laparotomy, which revealed a source in ~60%. No preoperative clinical and laboratory features, however, reliably predicted the likelihood of a positive result. CT imaging now detects most of the disorders previously uncovered only at operation, such as abscesses and malignancies, and, currently, exploratory laparotomy is rarely appropriate unless clinical, laboratory, or imaging findings persuasively indicate an intraabdominal process. Occasionally, however, laparotomy or laparoscopy may be necessary because some diseases, such as tuberculous peritonitis, necrotizing vasculitis, or peritoneal carcinomatosis can be present in the abdomen without producing any localizing symptoms, signs, or radiographic abnormalities.

Other diagnostic tests. When repeated histories, physical examinations, and investigations of the available clues remain unrevealing, sampling tissue from two areas may be profitable, even if they are not obviously abnormal by laboratory and imaging tests. Biopsies of the bone marrow and liver will each be diagnostic in ~15% of cases in this setting. In addition, elderly patients with an ESR of >40 mm/h should undergo early temporal artery biopsies, not only because giant cell arteritis is a common cause of FUO in this age group, but also because early recognition and treatment of this disorder can prevent the sudden blindness that it sometimes causes.

Radionuclide scanning in FUO is theoretically useful, but commonly disappointing or misleading in practice. Whether they employ indium-labeled leukocytes or polyclonal IgG, gallium-67, or technetium-labeled anti-granulocyte antibody, these scans have an impressive number of false-positive and false-negative results. Other techniques are usually better, because even a true-positive scan only indicates an area of increased uptake, but does not provide anatomic detail. Therefore, clinicians should rarely order these tests early in the course of investigation, they should cautiously interpret the findings, and they should ordinarily not recommend invasive procedures based solely on these studies.

Approach when the diagnosis remains obscure. If the source of the fever remains elusive after an initial evaluation, repeated histories and physical examinations are crucial in detecting new developments or uncovering information previously overlooked or unappreciated and are often more rewarding than further laboratory tests or imaging procedures. Each patient deserves a discerning, individualized approach. Use of algorithms is inappropriate, and one common mistake is to follow a preconceived protocol rather than investigate the abnormalities already uncovered. The paper by Petersdorf and Beeson [2] popularized Sutton's Law, originally enunciated by Dr. William Dock, which recommends performing the procedure most likely to yield a diagnosis, such as a biopsy of an enlarged lymph node or mass, rather than conducting a sequence of predetermined tests. The name of the law derives from the response attributed to the thief Willie Sutton when asked his reason for robbing banks, "Why, that's where the money is." Ironically, Sutton denied making the statement, which he deemed a fabrication of some enterprising reporter [15].

When all reasonable diagnostic approaches are fruitless and the patient's condition is stable, careful observation may be superior to further evaluation. Despite meticulous investigation, the cause of fever remains obscure in about 5%–15% of cases. A strikingly consistent finding in all series, however, is that most of these patients defervesce without treatment, and rarely does a serious disease emerge later.

This spontaneous resolution of fever in stable patients underlies part of a cogent argument against routine therapeutic trials, in which defervescence following institution of a medical regimen designed to treat a specific disorder supposedly establishes a diagnosis. For example, when fever in patients with self-limited illnesses coincidentally abates while they receive antimicrobial therapy for possible endocarditis or occult tuberculosis, physicians may erroneously conclude that the patients require protracted therapy with potentially harmful medicines.

Furthermore, treatment is rarely specific for a single disease; for instance, the aminoglycoside appositely chosen for treating putative culture-negative endocarditis also inhibits tubercle bacilli, and, although it might produce defervescence in tuberculosis, treatment of that infection with a single active agent is inappropriate.

In addition, the response of fevers in many diseases is unpredictable, often undramatic, and, occasionally, sluggish, a circumstance that may make both the patient and the clinician anxious about the wisdom and efficacy of the therapeutic regimen. In one study, for example, patients treated for culture-negative endocarditis remained febrile for an average of 11 days, and in some the fever lasted for >3 weeks [16]. Similarly, in one series of cases of tuberculosis, nearly 40% were febrile for >2 weeks after institution of therapy, and among this group the average time to defervescence was 1 month [17]. For these and other reasons, experienced clinicians discourage therapeutic trials, which often obfuscate rather than illuminate, except in special circumstances. In seriously ill or deteriorating patients, such empiric therapy may be prudent. The clinician, however, should obtain all appropriate diagnostic tests before proceeding and should choose a regimen with the narrowest spectrum of activity to ensure that a response to it has some diagnostic value. In critically ill patients, however, a broader-based therapy may be prudent to cover several possible causes, with modification later when the etiology becomes apparent.

Fever of Unknown Origin in Special Groups

Patients with known cancer. Studies conducted in the 1970s [18, 19] indicated that the cause of fever in about one-half of patients with known cancer and FUO was infectious and that in most of the rest it was the underlying malignancy. Gram-negative bacilli or fungi usually caused the infections, which typically occurred as a complication of neutropenia. When the fever arose from the malignancy, the tumor was characteristically extensive and progressive: solid tumors were usually widely metastatic, lymphomas had visceral involvement, and the patients had often noticed new masses, swellings, or enlarging lymph nodes.

FUO in patients infected with HIV. Among patients infected with HIV, FUO usually occurs with advanced disease, typically when the CD4 cell count is $<100/mm^3$. The cause of the fever is infectious in ~75% of patients. By far, the most common etiologic organisms identified have been mycobacteria—either *Mycobacterium tuberculosis* or non-tuberculous mycobacteria (predominantly *Mycobacterium avium* complex). Other microbes have included cytomegalovirus, *Toxoplasma gondii, P. carinii, Cryptococcus neoformans, Salmonella* species, *Leishmania* species (in studies from Spain and France [20, 21]), *Aspergillus* species, and varicella-zoster virus. Non-infectious causes, primarily non-Hodgkin's lymphoma and drug fever, account for ~10% of cases, and ~15% remain unexplained. Only rarely is HIV infection alone responsible.

The most useful diagnostic tests are blood cultures for identifying conventional bacteria, mycobacteria, and fungi; thoracic CT to detect mediastinal lymph node enlargement; a serum cryptococcal antigen, which is sensitive and specific for indicating disseminated infection with *C. neoformans;* and biopsies of bone marrow, liver, and abnormal lymph nodes. Biopsies of bone marrow and liver are particularly helpful in demonstrating mycobacteria and fungi by histology or culture: these procedures may be positive when blood cultures for these organisms are negative. Bone marrow examination, however, is less useful for detecting lymphoma.

Conclusion

Because of the requirement that the diagnosis remain elusive after 1 week of intensive investigation, FUO, by definition, is a challenging problem. Moreover, unlike Cabot's time [1], when most cases seemed restricted to a few diseases, primarily infections, the differential diagnosis of FUO now comprises >200 disorders and must be among the longest of any condition in medicine. Nevertheless, the venerable skills of a meticulous history, a thorough physical examination, discriminating use of investigative procedures, and constant reassessment of the evidence will usually reveal the cause. A paramount measure of a discerning clinician is knowing how to apply the available diagnostic tools appropriately and when careful, patient observation is better than further investigative or therapeutic interventions. Despite all the changes since Cabot's report early in this century [1], these principles remain constant.

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