Coxiella burnetii (as indicated above), *T. whipplei*, and *Bartonella* species. Marantic endocarditis is a sterile thrombotic disease that occurs as a paraneoplastic phenomenon, especially with adenocarcinomas. Sterile endocarditis is also seen in the context of systemic lupus erythematosus and antiphospholipid syndrome.

Of the NIIDs, large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still's disease are rather common diagnoses in patients with FUO. The hereditary autoinflammatory syndromes are very rare and usually present in young patients. Schnitzler's syndrome, which can present at any age, is uncommon but can often be diagnosed easily in a patient with FUO who presents with urticaria, bone pain, and monoclonal gammopathy.

Although most tumors can present with fever, malignant lymphoma is by far the most common diagnosis of FUO among the neoplasms. Sometimes the fever even precedes lymphadenopathy detectable by physical examination.

Apart from drug-induced fever and exercise-induced hyperthermia, none of the miscellaneous causes of fever is found very frequently in patients with FUO. Virtually all drugs can cause fever, even that commencing after long-term use. *Drug-induced fever*, including DRESS (drug reaction with eosinophilia and systemic symptoms; **Fig. 25e-49**), is often accompanied by eosinophilia and also by lymphadenopathy, which can be extensive. More common causes of drug-induced fever are allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, furosemide, antimicrobial drugs (especially sulfonamides, minocycline, vancomycin, β-lactam antibiotics, and isoniazid), some cardiovascular drugs (e.g., quinidine), and some antiretroviral drugs (e.g., nevirapine). *Exercise-induced hyperthermia* **(Chap. 479e)** is characterized by an elevated body temperature that is associated with moderate to strenuous exercise lasting from half an hour up to several hours without an increase in CRP level or ESR; typically these patients sweat during the temperature elevation. *Factitious fever* (fever artificially induced by the patient—for example, by IV injection of contaminated water) should be considered in all patients but is more common among young women in health care professions. In *fraudulent fever*, the patient is normothermic but manipulates the thermometer. Simultaneous measurements at different body sites (rectum, ear, mouth) should rapidly identify this diagnosis. Another clue to fraudulent fever is a dissociation between pulse rate and temperature.

Previous studies of FUO have shown that a diagnosis is more likely in elderly patients than in younger age groups. In many cases, FUO in the elderly results from an atypical manifestation of a common disease, among which giant cell arteritis and polymyalgia rheumatica are most frequently involved. Tuberculosis is the most common infectious disease associated with FUO in elderly patients, occurring much more often than in younger patients. As many of these diseases are treatable, it is well worth pursuing the cause of fever in elderly patients.

APPROACH TO THE PATIENT: Fever of Unknown Origin

FIRST-STAGE DIAGNOSTIC TESTS

Figure 26-1 shows a structured approach to patients presenting with FUO. The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history-taking and physical examination and the obligatory investigations listed above. *PDCs* are defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis. Although PDCs are often misleading, only with their help can a concise list of probable diagnoses be made. The history should include information about the fever pattern (continuous or recurrent) and duration, previous medical history, present and recent drug use, family history, sexual history, country of origin, recent and remote travel, unusual environmental exposures associated with travel or hobbies, and animal contacts. A complete physical examination should be performed, with special attention to the eyes, lymph nodes, temporal arteries, liver, spleen, sites of previous surgery, entire skin surface, and mucous membranes. Before further diagnostic tests are initiated, antibiotic and glucocorticoid treatment, which can mask many diseases, should be stopped. For example, blood and other cultures are not reliable when samples are obtained during antibiotic treatment, and the size of enlarged lymph nodes usually decreases during glucocorticoid treatment, regardless of the cause of the lymphadenopathy. Despite the high number of false-positive ultrasounds and the relatively low sensitivity of chest x-rays, the performance of these simple, low-cost diagnostic tests remains obligatory in all patients with FUO in order to separate cases that are caused by easily diagnosed diseases from those that are not. Abdominal ultrasound is preferred to abdominal CT as an obligatory test because of relatively low cost, lack of radiation burden, and absence of side effects.

Only rarely do biochemical tests (beyond the obligatory tests needed to classify a patient's fever as FUO) lead directly to a definitive diagnosis in the absence of PDCs. The diagnostic yield of immunologic serology other than that included in the obligatory tests is relatively low. These tests more often yield false-positive rather than true-positive results and are of little use without PDCs pointing to specific immunologic disorders. Given the absence of specific symptoms in many patients and the relatively low cost of the test, investigation of cryoglobulins appears to be a valuable screening test in patients with FUO.

Multiple blood samples should be cultured in the laboratory long enough to ensure ample growth time for any fastidious organisms, such as HACEK organisms. It is critical to inform the laboratory of the intent to test for unusual organisms. Specialized media should be used when the history suggests uncommon microorganisms, such as *Histoplasma* or *Legionella*. Performing more than three blood cultures or more than one urine culture is useless in patients with FUO in the absence of PDCs (e.g., a high level of clinical suspicion of endocarditis). Repeating blood or urine cultures is useful only when previously cultured samples were collected during antibiotic treatment or within 1 week after its discontinuation. FUO with headache should prompt microbiologic examination of cerebrospinal fluid (CSF) for organisms including herpes simplex virus (HSV; especially HSV-2), *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*. In CNS tuberculosis, the CSF typically has elevated protein and lowered glucose concentrations, with a mononuclear pleocytosis. CSF protein levels range from 100 to 500 mg/dL in most patients, the CSF glucose concentration is <45 mg/dL in 80% of cases, and the usual CSF cell count is between 100 and 500 cells/μL.

Microbiologic serology should not be included in the diagnostic workup in patients without PDCs for specific infections. A TST is included in the obligatory investigations, but it may yield false-negative results in patients with miliary tuberculosis, malnutrition, or immunosuppression. Although the interferon γ release assay is less influenced by prior vaccination with bacille Calmette-Guérin or by infection with nontuberculous mycobacteria, its sensitivity is similar to that of the TST; a negative TST or interferon γ release assay therefore does not exclude a diagnosis of tuberculosis. Miliary tuberculosis is especially difficult to diagnose. Granulomatous disease in liver or bone marrow biopsy samples, for example, should always lead to a (re)consideration of this diagnosis. If miliary tuberculosis is suspected, liver biopsy for acid-fast smear, culture, and PCR probably still has the highest diagnostic yield; however, biopsies of bone marrow, lymph nodes, or other involved organs also can be considered.

The diagnostic yield of echocardiography, sinus radiography, radiologic or endoscopic evaluation of the gastrointestinal tract, and bronchoscopy is very low in the absence of PDCs. Therefore, these tests should not be used as screening procedures.

After identification of all PDCs retrieved from the history, physical examination, and obligatory tests, a limited list of the most probable diagnoses should be made. Since most investigations are helpful only for patients who have PDCs for the diagnoses sought, further diagnostic procedures should be limited to specific investigations aimed at confirming or excluding diseases on this list. In FUO, the