

Infectious Dis

FUO (FEVER OF UNDETERMINED ORIGIN): NOT WHAT IT USED TO BE

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A. Characteristics of FUO (1)

1. Illness of more than 3 weeks duration
2. Documented temperature higher than 101° Fahrenheit or 38.3° Centigrade on several occasions
3. Uncertain diagnosis after 1 week of study in the hospital.

B. Changing spectrum of diseases in patients with FUO. Infectious causes of FUO remain a significant minority although the specific etiologies have varied over the past decades (Table 1) (1-4). Recently, viral infections have been noted to increase in frequency whereas mycobacterial infections, endocarditis and malaria have decreased as a significant contributor in series of FUO cases. Localized infections such as abdominal abscesses are just as frequent as before, but more series have also noted infections such as sinusitis, osteomyelitis, catheter infection and vascular graft infections. In some series, the frequency of neoplastic diseases as a cause of fever has increased (4). The types of tumor include as before non-Hodgkin's lymphoma, leukemia (particularly pre-leukemic leukemia) and solid tumors, but also a variety of rarely seen reticuloendothelial malignancies such as malignant histiocytosis and angio-immunoblastic lymphadenopathy. Adult Still's disease has recently been recognized as a febrile connective tissue disease in older adults but a decrease was found in the frequency of systemic lupus erythematosus as a cause of FUO due to earlier diagnosis with serologic tests (4). More cases were seen with granulomatous hepatitis, but these patients had non-specific presentations, tended to follow a benign course, and frequently resolved spontaneously (4). Recently it has been recognized that not only patients with abdominal trauma leading to retroperitoneal hematomas may present with fever but also prolonged fever may be seen in patients with dissecting aneurysms (5,6).

Table 1. FUO over the years (%)

	Yale (1) 1952-1957	Cleveland (2) 1959-1960	Scott & White (3) 1969-1976	Seattle (4) 1970-1980	Dallas 1979-1985
Infections	36	21	37	30	50
Neoplastic Disease	19	6	31	31	15
Connective Tissue Disease	13	13	19	8	5
Miscellaneous	25	20	8	17	22
Not Diagnosed	7	40	5	12	8

One might ask why do the entities which have been historically associated with FUO continue to be the same ones which predominate in recent series, such as abdominal abscesses, urinary tract infection, post-operative or surgical infections (Table 2) (1-4). These entities may have such subtle localizing features and the generalized symptoms may be so prominent that the abdominal or surgical site is not recognized as the likely cause. In particular, the great majority of elderly patients have non-specific symptoms with few localizing findings (7). Secondly, repeated immunologic, serologic, and microbiologic tests may remain negative (4). In particular, skin tests had a significant false positive and false negative rates. Thirdly, initial studies to localize a site of infection by radiography, scans or computerized tomography fail to prove a clue (Table 3). Only 26% of all scans were helpful in diagnosis whereas 16% were falsely positive and 10% falsely negative (4). Ultrasonography was only helpful in 25% and none of 8 CT scans contributed to a final diagnosis with 3 false negative and 1 false positive. Finally, biopsies of tissue may not always be helpful (4). Bone marrow and liver biopsies had a low diagnostic yield. Hematologic malignancies and tuberculosis were diagnosed by bone marrow biopsy and granulomatous hepatitis was recognized with liver biopsy; however, no patient with lymphoma or reticuloendothelial malignancy was proven by liver biopsy. Biopsies of tissue that were abnormal such as lymph nodes, muscle, or bone were more helpful in the diagnosis. Exploratory laparotomy has previously been touted as useful with a 66% likelihood of success in series reviewed prior to the 80's (8). The chances were greater in those with abdominal tumor or intrabdominal abscesses. However, laparotomy was normal in a number of cases and was abnormal without being diagnostic in an equal number. Hence only in those with strong, suggestive clinical evidence of abdominal disease would an exploratory laparotomy be of assistance. Presently, if ultrasonography or CT shows intrabdominal disease, CT directed aspiration or biopsy at laparoscopy may be helpful. Finally, patterns of disease may be overlooked as attention is paid to individual organ system involvement. This is particularly true of connective tissue diseases and miscellaneous diseases such as polymyalgia rheumatica, in which the overall pattern is more indicative than a localizing event. These entities were frequently diagnosed after long periods of follow-up with clinical features providing the clue (4).

**Table 2. Comparison of Entities Responsible for FUO
as Seen by a Single Author (Petersdorf) and at DVAMC**

	Yale (1) 1952-1957	Seattle (4) 1970-1980	Dallas 1979-1985
Infections	36	32	40
Abscess	11	11	7
Mycobacterial	11	5	4
Viral (esp. CMV)	0	4	8
UTI	3	3	7
Post-op Infection	0	1	4
Endocarditis	5	0	4
Other Infections	6	8	6

Table 3. Helpful Tests: Seattle, 70-80)

	(%) Helpful in diagnosis	False Positive	False Negative
Ultrasound	25	0	12
Liver-Spleen	15	0	5
Gallium Scan	17	20	7
CT Scan-Abdomen	0	12	38

C. FUO at DVAMC

Cases evaluated by the Infectious Disease Section, Medical Service, DVAMC from 1979 to 1985 were reviewed (Table 4).

- 1 - to compare frequencies of entities with other series
- 2 - to update more useful tests of value in our medical center
- 3 - to review patterns of certain systemic disorders which present as a diagnostic dilemma for Infectious Diseases consultants and internists.

a - Criteria were modified slightly to include certain cases of less than 3 weeks if no obvious clue was present at time of consultation with Infectious Disease Section at DVAMC. Cases of FUO were analyzed whether seen in consultation 3 days or 3 weeks after admission.

b - If uncertainty existed at time of discharge as to cause of FUO, a follow-up analysis was done. In addition for purposes of discussion, a few cases have been borrowed from other periods and from other hospitals to illustrate aspects of workup or therapy.

c - Virtually all these patients were male which may lead to bias in the frequency of certain entities.

d. The series represents cases admitted to a hospital which functions as a primary and secondary care center. Consequently cases represent those patients likely to be encountered by any physician or internist who may require an Infectious Disease consult for assistance if initial studies are negative.

D. Details of FUO at DVAMC - Viral Infections**1. Viral Infections**

Cytomegalovirus (CMV) (3 cases) and EB virus (2 cases) were the most common of the viral infections in which fever persisted for longer than the usual 2-3 week limit expected with viral infections. As noted in reviews of CMV mononucleosis, fever and other symptoms may last from 2-6 weeks (9). Most of these 5 individuals had a history of homosexual preference but did not have findings consistent with HTLV-3 infection or AIDS save in one case. Pyrexia of undetermined origin has been reported in patients with AIDS who had CMV inclusion bodies in multiple organs at autopsy (10). Although this case also had cerebral lymphoma, toxoplasma CNS infection and lung abscess at autopsy, CMV infection could have explained the protracted fever of 5 months duration. Clues to CMV and EB virus may include atypical mononuclear cells and hepatic enzyme abnormalities. CMV can be isolated from urine of patients up to 24 weeks after the illness begins as well as from circulating leukocytes (9, Dr. Luby, UTHSCD). CMV antibody is usually present in high titer ($>1:256$) on the earliest serum tested in proven cases. Very high EB virus antibody ($>1:512$) with negative monospot was seen in 1 of the 2 cases with EB infection, whereas the other case required more than three weeks for monospot to become positive (11). Toxoplasmosis also can present as a cause of the mononucleosis syndrome with protracted fever, proven by an IFA $>1:512$ (12).

Table 4. Causes of FUO at DVAMC 1979-1985

Fever without obvious cause: Excluded if obvious localizing infection as pneumonia, UTI, CNS.

Total: 80 cases seen by Infectious Disease Section

a. Infection	Total 40	Specific Entities	Tests Helpful in Dx
Viral	8	CMV, 3EBV2	Serologic
UTI	7	>80 or demented 6	Urine C&S (repeat), Sono
Abscess	4	Abdominal 3 (1 in carcinoma)	CT
Endocarditis	4	Prosthetic valve 2, small GNR 1, lymphoma 1	Repeat Bd Cult. Hold for > 1 week
Mycobacterial	4	TB in 3; MAI with Hairy cell 1	Bone marrow: granuloma, AFB, Fungus cultures
Vascular graft infections	3		CT
Osteomyelitis	3	Infected prosthesis 2	Bone scan with Gallium
Fungal	3	Candida 2, Histoplasmosis 1	Blood, urine cultures
Tularemia	2	Hx tick bite, rabbit hunting in December	Serologic
Relapsing fever	1	"Cabin fever"	Blood smear
Dental	1	Fever, pain with eating	Hx, x-ray
b. Other	33		
Tumor	12	Solid 10 Lymphoma 2	Therapeutic test: NSAID CT, repeat CT, biopsy
Drug	5	Quinidine 2, aldomet 1	Look at medicine list
Hepatitis	6	Alcoholic 5, granulomatous 1	Biopsy (Dx of exclusion)
Hematoma	2	Postbiopsy, retroperitoneal	Take a history! Elevated protime
Pul. emboli	2	Stroke 1, postangio 1	Consider possibility
Phlebitis	2	Drug abusers	R/O BE first, Aspirate vein
Stroke	2		Difficult to sort out
Pericarditis	2	Nonspecific or with Still's	Echo; ASA or NSAID response (steroid in some)
c. Unknown	7	No obvious cause, occasionally recurrent	Don't be afraid to follow without answer

2. Urinary Tract Infection

The diagnosis of urinary tract infection was delayed in 7 of our patients in spite of intermittently positive urine cultures in elderly or demented individuals. Part of the confusion and delay in diagnosis was the empiric use of antibiotics which did not eradicate the infection nor ameliorate symptoms. Perhaps the age and central nervous system findings prevented the appreciation of signs of inflammation normally expected in patients with pyelonephritis. However, we have seen men in their 50's who present with persistent bacteremia due to a prosthetic abscess who had no physical complaints until a prostatic exam was performed. Most of the cases in the recent review from Seattle indicated that those with urinary tract infection had anatomic abnormalities of the kidney leading to obstruction (4). None could be found, however, in our cases other than the usual mild obstructive changes in elderly men; in fact many of the patients had indwelling catheters intermittently or continuously during the period of observation. Ultrasonography was of minimal help in most of these cases although it can be a useful test in the diagnosis of intrarenal or perinephric abscess (13). Perhaps two additional explanations account for these cases in our series.

a. An intrarenal focal infection (lobar nephronia) or intrarenal abscess can account for persistent infection (13,14). Intrarenal collections can occasionally be aspirated with a CT-directed needle puncture (13).

b. The usual intrarenal concentrations of antibiotics alone may not be sufficient to eradicate the organism or decrease signs of inflammation. With significant renal infection, studies in our laboratory have shown that macrophages accumulate in the kidney and ingest large numbers of organisms. Since antibiotics may only penetrate macrophages minimally, perhaps the organisms persist intracellularly with persistent production of interleukin-1 (aka leukocyte pyrogen) (15). We have found frequently that cases with persistent fever on a single antibiotic, respond to the addition of a beta-lactam (preferably ampicillin or ureidopenicillin over cephalosporin) to an aminoglycoside. In experimental pyelonephritis, the combination of an effective beta-lactam with aminoglycoside is the only therapy associated with eradication of organisms from the infected kidney (16). Hence in elderly persons with persistent fever, we would recommend repeat urine cultures, careful prostatic evaluation (with culture of expressed prostatic secretions), or if fever persists on a single antimicrobial agent: add combination therapy while doing studies to evaluate for abscess or nephronia. Since men relapse much more frequently with shorter courses of therapy than do women, plan on 3-6 weeks total therapy. (17).

3. Localized Infections.

Of the four patients with an abscess, abdominal abscesses were present in 3 patients, including individual cases of liver abscess, pancreatic abscess, and a malignant solid tumor which became secondarily infected. In addition a single case was seen with a thigh abscess that was unrecognized for a long period. Localized infections were also found at the site of vascular graft in 3 patients and in joint prostheses in 2 cases. Most of these localized infections were with gram negative organisms. Symptoms at the site of infection in all cases were minimal so that the surgical site was not suspected as the likely source of infection. Hence, Petersdorf's Law must be invoked: "When the diagnosis is obscure, look at the surgical scar for sure"

(4). However, one particular case of an infected hip prostheses presented with minimal localized symptoms but in fact had Brucella abortus infection of his hip prosthesis. Only after a history was obtained of the loss of 90% of his herd of cattle due to Bang's Disease (which he was not informed by the agricultural workers could spread to humans) were appropriate studies with brucella titers done and the diagnosis made (18). He responded to intermittent courses of tetracycline over a 3 year period but had a persistently positive bone scan. The infection was cured only after the prosthesis was removed and he was given an intensive course of 6 weeks tetracycline with streptomycin followed by 6 months of tetracycline alone. If we saw a case of brucella now, we would preferably treat with a combination of tetracycline or doxycycline and rifampin or use long term trimethoprim sulfamethoxazole (TMP/SMX) (19). A Spanish group has reported equal success rates with either, although more frequent side effects were noted with TMP/SMX. In conclusion:

- if the patient with fever has a previously inserted prosthesis or graft or recent surgery: consider that as the infected site,
- if intrabdominal: do CT scan,
- if extremities: do a bone scan with gallium scan to follow,
- if abnormal: CT directed aspiration of abdominal abscesses or open biopsy of bony sites.
- if pain on eating: x-ray teeth.

An alveolar abscess may not be apparent on a routine history or physical exam. One of our patients did indeed have pain on eating but was not severe enough for him to bring this to his physician's attention until dental exam done routinely at DVAMC revealed infected teeth with an apical abscess. His symptoms promptly responded with tooth extraction. One of our more famous cases of recurrent fever prior to this series was diagnosed by Dr. Knochel at the VA. This patient was admitted to rule out relapsing fever due to borrelia since he resided in Denton County, a site of a previous reported case by Dr. Southern (20). His history, however, revealed fever on Monday mornings approximately every 2 weeks, which coincided with away Dallas Cowboys games (before the blackout rule was amended). Further history taking by our superb chief revealed that he always watched the games on television with a large bowl of popcorn with significant fever that evening and the next day. He had multiple apical abscesses which responded promptly to tooth extractions.

Some have attempted to categorize FUO in the elderly (greater than 65 years of age) as being different than FUO in younger adults (7). However, similar major categories are present in elderly as in other age groups. Elderly persons with FUO due to abdominal abscess more frequently have no previous history of surgery and may have minimal symptoms other than fever to lead one to suspect abdominal abscess. Hence the physician should utilize scanning tests more frequently and perhaps earlier in the elderly person than in a younger adult in the absence of symptoms referable to the abdomen.

4. Bacterial endocarditis. A total of 4 cases were seen at the DVAMC including group B streptococcus and Staphylococcus epidermidis respectively in 2 patients with prosthetic valves who had low grade symptoms and presented late in their course. In two cases, endocarditis was not recognized on presentation because they had fever with other localizing signs. One elderly man presented with fever, abnormal liver function studies and hip pain. He

was thought to have osteomyelitis until blood cultures grew a small, gram-negative bacillus. After a week, it was finally identified as Actinobacillus actinomycetemcomitans, a causative agent of endocarditis which may require more than 7 days to grow or be identified. In the other patient, Bacteriodes fragilis was the cause of endocarditis in a patient with lymphoma. This patient failed to respond to treatment with bacteriostatic antibiotics because it was not appreciated that he had endocarditis until he developed evidence of a splenic abscess in the third week of treatment. Institution of therapy with IV metronidazole resulted in his becoming afebrile although he succumbed to another infection before therapy could be completed. Perhaps endocarditis is less commonly reported now than previously as a cause of FUO because physicians readily obtain blood cultures in any patient as a standard workup for fever. In fact, bacterial endocarditis along with malaria should not be in lists of FUO since these entities should be suspected and ruled out early in the evaluation of the febrile patients.

In none of the cases of endocarditis were more than 2 blood cultures required for establishment of the diagnosis; in fact, in virtually all cases seen at the DVAMC in the last 12 years one of the first two blood cultures has been positive in those proven to have bacterial endocarditis. I can recall only one case of endocarditis who came to autopsy at the VA who had negative blood cultures. In this case, blood cultures were drawn after institution of antibiotics in a person with end stage renal disease. He had originally presented with abdominal manifestations and no temperature elevation so he was treated for an acute abdomen with antibiotics. At post-mortem examination he had endocarditis. A peritoneal fluid culture had grown enterococcus, the presumed etiologic agent. One of the first two cultures with endocarditis will be positive 98% of the time; even if antibiotics have been administered, 91% of blood cultures will be positive. Three blood cultures were required to diagnose endocarditis in 100% of cases if no antibiotics were given and were sufficient in 11 of 13 on antibiotics (21). Repeated blood cultures are futile and represent a great deal of wasted time, effort and money (4). If the diagnosis of bacteremia or endocarditis is not forthcoming within 2-3 days of submission of the cultures, then request the Microbiology lab hold the blood cultures for a period of 2-3 weeks. Individual cases of endocarditis caused by slow growing gram-negative bacteria organisms (which may require incubation >7 days) have been reported (22). These appear as small gram negative coccobacillary forms and may not be identified for some weeks (Table 5). If the patient has received antibiotics, then request the lab for special media containing antimicrobial removal device such as 16 B medium which contains resins to remove antibiotic. The yield of positive cultures from patients on antibiotics has been reported to be improved with these techniques in individual cases with sepsis due to Staphylococcus aureus, streptococcus and a variety of aerobic and anaerobic gram-negative bacilli (23). Certainly there is no reason to draw more than three blood cultures in febrile individuals for whom no answer is available, unless a new process has developed or unless recent antibiotics have been administered.

Table 5. FUO Which Turns Out to Be Endocarditis

Certain microorganisms require 7d for growth or identification

Haemophilus parainfluenzae

Haemophilus aphrophilus

Cardiobacterium hominis

Eikenella corrodens

Actinobacillus actinomycetemcomitans

So: Draw two cultures; request hold two weeks!

5. Disseminated infections without localizing features. This comprises one of the larger categories with multiple, potential pathogens being responsible. In our series, responsible pathogens included Mycobacteria tuberculosis, Mycobacteria avium-intracellulare (MAI), various fungi (Candida albicans causing esophagitis, urinary tract infection, and Histoplasma capsulatum in an AIDS patient), Francisella tularensis, Brucella abortus (see case of hip prosthesis infection above) and relapsing fever. No simple rule applies to establishing the diagnosis in any of these cases. A history can be helpful as in the 2 cases with tularemia: One patient presented with a protracted illness and unilateral axillary adenopathy. Prior to performing a left node biopsy to rule out lymphoma, a history of possible hunting exposure prompted Dr. Sheehan to recommend a tularemia titer, which was diagnostic. The other case was a telephone line operator who had reported increased tick exposure during his work but had no localizing lesion other than bilateral inguinal adenopathy. His initial titer was indeed negative but he had a clinical response to tetracycline (given to treat both Rocky Mountain Spotted fever and tularemia). This drug is effective in mild cases but streptomycin may be required in severely ill cases (24). Only when he reported to clinic some weeks later was a tularemia titer positive 1:256. However when we attempted to report this finding to him, we were informed that his telephone was not in service. Ironically enough, a few years ago his family had failed to pay the telephone bill so he was sent by the telephone company to remove his own telephone. A history of residing in a cabin on a hunting trip was useful in establishing the diagnosis of relapsing fever in our one case - Since tick-borne relapsing fever endemic area includes Texas, a history of exposure to the night-feeding wood tick and then demonstration of spirochites is diagnostic (25).

We have emphasized for years the importance of bone marrow biopsy as a diagnostic test in disseminated histoplasmosis but it can be a useful test in the diagnosis of tuberculosis in adults (26). However our yield in bone marrow examinations done exclusively for FUO evaluation is in the area of the batting average of Biancalana prior to recognition by David Letterman this summer. We can proudly report the recognition of presumed mycobacterial infection in 2 patients with aplastic anemia who had granulomas noted in repeat bone marrow samples after failure of other workup for FUO. Each had a prompt therapeutic response to antituberculous therapy. In addition a patient with hairy cell leukemia had disseminated MAI, an association previously described from our institution (Table 6) (27). A patient with AIDS with protracted fever had Histoplasma capsulatum demonstrated in the bone marrow. So although the bone marrow culture is a low yield procedure, it can be helpful in an occasional case and prevent further diagnostic and therapeutic procedures. Certainly the test is indicated if patients with underlying hematologic disorders develop fever. However, if bone marrow examination and cultures are negative, that does not necessarily rule out disseminated mycobacterial or fungus infection. In a recent report from Spain, (Table 7) tuberculosis was the most common infectious cause of FUO but in most cases, biopsy of tissue at time of peritoneal laparoscopy or of lymph nodes were required to establish the diagnosis (28). It is worth noting that the other causes of FUO in Spain include a multitude of infections requiring serologic and microbial tests (Table 7). The following case kindly provided by Dr. Ed Goodman illustrates the need for repeated biopsy and culture of tissue in cases with prolonged fever.

Table 6. Relative Frequency of Infections with Hairy cell Leukemia and other Malignant Neoplasms (27)

Type of Infection (%)	Hairy cell Leukemia	Chronic Lymphocyte Leukemia	Acute Leukemia	Hodgkin's Disease
Pyogenic	48	44	86	65
Nonpyogenic	34	7	14	35
Mycobacterial	4	0	0	1
Fungal	14	0	14	12
Viral	13	7	0	20
Parasitic	3	0	0	2
Unspecified	18	49	0	0

This page has been redacted from the publicly-available protocol due to privacy issues.

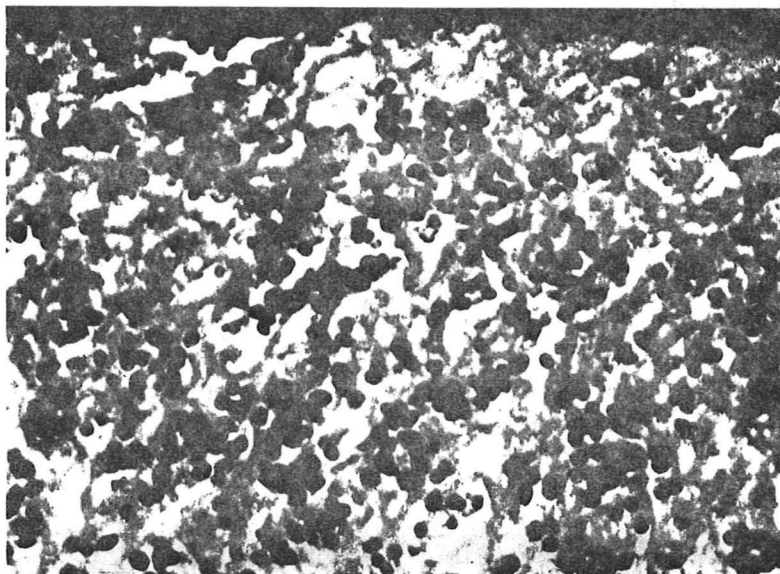


Figure 1. Mesenteric lymph node with histoplasma.

Table 8. Causes of Prolonged Fever (> year) (29)

Osteomyelitis
Subphrenic abscess
Malaria
Whipple's disease
Renal cell carcinoma, adenoca of colon
Regional enteritis
Granulomatous hepatitis
Vasculitis: Periarteritis nodosum, polymyalgia rheumatica,
juvenile rheumatoid arthritis (Still's disease)
Fabry's disease

6. Neoplastic diseases. Twelve cases of FUO in our series were due to neoplasms with solid tumors predominating (10). Perhaps the lower frequency of Hodgkin's and non Hodgkin's lymphoma in this series is due to the early recognition of patients at this hospital and because fewer of our cases are referred from other hospitals than perhaps is true in Seattle (4). Nevertheless, the recognition of solid tumors was made following ultrasonography or CT in most cases, as was the diagnosis of Hodgkin's disease during this period. Survival in our patients with solid tumors was short (2 months or less in most cases) but fever frequently persisted after a tissue diagnosis was made. None of the patients with solid tumors was given chemotherapy. Consequently, we resorted to the use of non-steroidal anti-inflammatory agents (NSAID) since this has been reported recently to be successful in patients with fever due to malignant diseases (30). Figure 2 shows the prompt response of fever in a patient with metastatic rectal carcinoma who was unsuccessfully treated with antibiotics but responded promptly to naproxen 250 mg twice a day. Patients with infection will not respond to NSAID. We would not regard this as a diagnostic test but as therapy for those with carcinoma who do not have an obvious infection but who are suffering from fever, chills, and sweats.

7. Drug therapy. Drug therapy as a cause of FUO is infrequently seen in most series but may be baffling, particularly in hospitalized patients who receive drugs not commonly recognized to cause fever. In our cases, 2 of the cases were due to quinidine. In particular, one patient had significant liver function abnormalities which led his physicians to consider infectious etiology although it is well known that quinidine can cause granulomatous hepatitis with fever (31). Cimetidine, a commonly used drug, has been reported to cause long lasting central fever which promptly responds to discontinuation of the drug (32). Hence, looking at the patient's chart and recognizing that many drugs can lead to fever is an important step. Recently Kauffman has emphasized that a number of drugs can cause FUO in the elderly (Table 9) so these particularly bare noting by any busy clinician (7).

Table 9. Commonly Used Drugs That Cause FUO (7)

Antihistamines
 Barbiturates
 Cimetidine
 Hydralazine HCl
 Ibuprofen
 Iodides
 Methyldopa
 Nitrofurantoin
 Procainamide HCl
 Quinidine
 Rifampin
 Salicylates
 Sulfonamides
 Penicillins
 Phenytoin sodium

8. Hepatitis. Six cases had fever in association with hepatitis including 5 of whom with excessive ethanol intake and no other explanation for the fever. Tisdale and Klatskin reported years ago that persons with alcoholic liver disease may have protracted fever even continuing after the patient's discharge from the hospital (33). They showed a correlation between parenchymal infiltration with polymorphonuclear leukocytic infiltrate in areas of active necrosis in the liver and significant temperature elevation in most of these cases. Although multiple entities can cause granulomas in liver, an entity known as granulomatous hepatitis has been responsible for recurrent long standing FUO (29,34). In one case, noncaseating granulomas were detected in the liver in a patient in whom all other studies were negative. This illness in this case presented in a non-specific fashion, followed a benign course, and resolved spontaneously (4).

9. Miscellaneous causes of FUO. Our miscellaneous category differs from that reported by others, illustrating the diversity of illnesses associated with protracted fever (3,4). Perhaps the two most difficult to establish are cases who have hematomas and patients with strokes. Patients with fever secondary to a hematoma may require multiple surgical procedures to prove this is the cause and even after surgery, the hematoma may not be recognized as the cause of fever in the case. Patients with stroke may continue to have fever with no obvious infectious etiology. In some of our cases, urinary tract infection was ultimately established as the cause but in 2 other cases, no answer for the cause of the fever was ever noted. Certainly mental confusion can occur as a response to fever in older patients, termed "beclouded dementia". Hence it is not possible to know if a person with stroke with fever has an infectious cause or whether the fever may be secondary to the central nervous system disease causing the stroke. This differentiation has led to some of the most frustrating experiences in the past 5 years of evaluating patients with fever. Recurrent pulmonary emboli has been noted frequently to cause fever (35). We have in fact noted very high temperature for a long period of time to be due to pulmonary emboli with or without infarction. Two cases of phlebitis with no obvious infection were noted in drug abusers. Endocarditis was, of course, ruled out initially. Presumably the phlebitis resulted from toxins present in the drug(s) but no proven cause was demonstrated. Finally, 2 cases of patients with pericarditis were shown to have fever: no etiology was found in 1 case but was presumably due to a viral infection (mycobacterial infection was ruled out). The other case had a clinical finding which defied explanation for some time until it was appreciated that his pattern fit a recently described clinical entity.

M.M. was a 47 year old black male who presented in June with 5 days history of sore throat, fever, and myalgias and 2 days of nausea, vomiting, and right upper quadrant pain. He continued to be febrile over the next 3 weeks, as his illness evolved. His previous history was interesting in that he told us on admission that he had adult arthritis diagnosed in 1972 while stationed in Southeast Asia. He had presented with polyarthrititis involving knees, wrists, and ankles with fever, hepatomegaly, and anemia. Extensive evaluation included tests for rheumatoid factor, bone marrow examination, and abdominal scans were unrevealing. He was placed on indocin with prompt defervescence. He had negative x-rays at the time. He did well in the intervening 13 years except for the development of insulin-dependent diabetes

mellitus. With the onset of illness, he noted severely swollen joints with the involved joints varying daily. Two days before admission he noted pain in his right upper quadrant which was made worse on taking a deep breath. On physical exam on admission he had a temperature of 101° F, beefy red pharynx without exudate, a pericardial rub, and a swollen red right knee and ankle. He also had a confluent macular rash over his abdomen and arms which was present at the height of his temperature elevation but disappeared in the morning when his temperature was normal. His chest x-ray showed interstitial markings and a pO₂ at room air was 53. His hematocrit was 30 with normochromic, normocytic indices and an ESR of 35. His white count on admission was 26,500 with differential showing 70% segs, 2% bands and 19% lymphocytes. The total blood cell white count reached a peak of 49,000 on the 5th day of admission with a persistent left shift. He had an elevated bilirubin (1.8 mg/dl) and alkaline phosphatase of 132 (normal 115), but otherwise normal liver function tests. All serologic tests including rheumatoid factor were negative and multiple microbiologic cultures were negative. He was treated with aspirin on admission with no response and then indomethacin. However, this was discontinued after he developed guaiac positive stools. He continued to have temperature spikes again with an elevated white count. He developed a persistent pericardial rub and became short of breath. Cardiac cath was done which showed a normal ejection fraction of .6, normal left ventricular function, "clean" coronary arteries and no valvular disease. A myocardial biopsy was obtained which showed normal myocardium. Because of the presumptive diagnosis of adult Still's Disease, he was begun on high dose steroids with prompt resolution of all symptoms including joint complaints and fever. He has done well in the clinic as steroids have been tapered. However, he continues to be short of breath and pulmonary functions reveal a persistent restrictive defect.

This patient depicts a diagnostic dilemma of adults with rheumatoid factor negative polyarthritis (36). A number of reports recently have summarized the clinical and laboratory features of patients with adult Still's Disease (36-39). Although there is no pathognomonic abnormality, the condition can be readily recognized by the pattern of presentation. All of the patients presented with the following: evening spikes in temperature, severe arthralgia and myalgia which were worse during febrile periods, severe sore throat, neutrophilic leukocytosis, normochromic and normocytic anemia, increased ESR and a rather typical rash which is an erythematous, evanescent maculopapular rash over the trunk or extremities which appears with the fever and subsides as the fever subsides (Table 10) (38). The fever characteristically shows an evening spike with return of the temperature to normal the following morning. Arthralgias are present virtually in all cases, but the arthritis may be fleeting and be overshadowed, as in our case, by the prominent systemic features. However, cartilage loss or erosions may become evident; our case developed carpal ankylosis (39). Adenopathy, splenomegaly, pleuritis, and pneumonitis may be less frequently seen. Pleuritis has been noted in 30% and pericarditis in 25%. Although patients may initially respond to salicylates, rarely do they respond completely and most require additional therapy either with high dose non-steroidal anti-inflammatory drugs or even prednisone in a small proportion of cases (38). Our case represents one of the oldest cases at 47 although he had had a previous attack. In fact,

recurrences are quite commonplace with most having a chronic course characterized by remissions and exacerbations of arthritis associated with fever and rash (39). He also sets a world record for the highest white count to be found in a case of adult Still's Disease (application for the Guinness Book of Records has been submitted).

Table 10. Characteristic Findings in Adult Still's Disease (38)

Clinical %	Laboratory %
Arthralgia 98	ESR 100
Typical rash 90	WBC 97
Arthritis 88	Anemia 92
Fever 83	Albumin 85
Sore Throat 50	WBC 18,000 67
Adenopathy 48	IgG 48
Splenomegaly 45	ANA 4
Pulmonary 31	Rheumatoid Factor 2
Pericarditis 26	

10. Unknown and undiagnosed. A total of 7 cases had no known cause for FUO determined. In all of these cases, the fever resolved within 4-5 weeks, although not always by time of discharge from DVAMC. Review of these records indicated no further difficulties with fever in the future. We have seen patients in the past who had recurrent episodes of protracted fever, but this appears to be a less common entity presently (40,41). In a recent series, after follow-up for more than five years of 34 cases with no cause for FUO established at time of initial evaluation, a diagnosis was ultimately made in fewer than 10% of cases (41). Hence, if the patient appears to have a benign course and no prompt answer is available, it is wisest not to expend a great deal of effort and money in achieving an etiologic diagnosis. Finally, a prolonged febrile illness in an older individual may be suggestive of the clinical entity, polymyalgia rheumatica (42,43). Since no proven test is available for this entity, it is counted as a recurrent, undiagnosed FUO (4).

Case #4 - G.M. is a 62 year old white male with a history of peptic ulcer disease and TIA's who was admitted with a 2 week's history of fever, malaise, and myalgia. He had been followed by another physician who attributed the fever to prostatitis but had found that his temperature did not respond to 2 different antibiotics. He was referred to the Dallas VAMC for further evaluation where his temperature persisted for the first 10 days of admission. He had no travel history or exposure to individuals with TB or other infectious diseases. He had generalized weakness, with proximal muscle weakness principally on the left side. His ESR was 121, but other serologic studies were negative. Chest CT showed pleural disease, right greater than left but no free fluid. He had abnormal liver functions with alkaline phosphatase of 391, a leucine amino peptidase of 35, (normal 22). Abdominal sono showed echogenic mass in the left lobe of the liver measuring 3x3 but

abdominal CT failed to demonstrate any liver abnormality. Since his temperature continued to be elevated and since he had hepatic function abnormalities, a peritoneoscopy was performed with biopsy of the superficial lesion on the left lobe of the liver. Pathologic diagnosis was cavernous hemangioma. Fortunately he had no complications post biopsy. Because he had been thought possibly to have a neoplasm as a cause of the fever with the abnormal liver function, he had been given naproxen 250 mg BID (see above for use in malignancy). When the microscopic examination revealed no malignancy, the drug was discontinued. A single day of the anti-inflammatory agent was sufficient to render him afebrile during remainder of hospitalization. His appetite improved as did his weakness. Rheumatologic consultation recommended a temporal artery biopsy which the patient refused but agreed to consider as an outpatient. He was discharged on non-steroidal anti-inflammatory drugs to take prn fever.

The major presenting symptom of polymyalgia rheumatica is pain and morning stiffness, particularly of shoulders (42). Less frequently, tenderness of shoulders or upper arms is seen - a small proportion may have malaise, fatigue and weight loss. Fever can be persistent: in a series of 5 cases compiled by Dr. Tompsett at BUMC, fever in polymyalgia cases persisted for up to 5 months. A biopsy of temporal artery was positive in 3 of 5 of his cases, whether or not they had significant headache or cranial pain. However, fewer than 20% of a recently reported group of patients had a positive biopsy, and all had signs or symptoms of arteritis (42,43). The median duration of illness was 11 months and therapy with either non-steroidal anti-inflammatory drugs (NSAID) or corticosteroids was successful in decreasing ESR and symptoms. The patient has been seen in clinic and has no evidence of arteritis. He will be followed closely in clinic with ESR checked periodically and response to therapy with disalcid observed (continuous NSAID contraindicated due to prolonged PUD history).

11. Factitious Fever and self-induced Infection

No case of factitious fever were seen at DVAMC although we have seen recently a possible case of self-induced osteomyelitis. Patients with factitious fever have severe underlying personality disorders, frequently characterized by dependency, poor impulse control and hostility (44). In addition they may manifest other psychiatric illness episodically, as conversion reactions, depression or transient psychoses. Some patients may induce severe factitious illness by self-inoculation of contaminated materials. In particular, local tissue infections (our recent case) may be particularly difficult to treat because they can manipulate or contaminate their wounds. Caution has to be used in confronting patients with evidence of their illness. A plan for social/psychiatric care needs be in operation and the patient treated in a straightforward, non-accusatory manner. The confrontation frequently results in anger and rage directed at the attending physicians (44). In addition the adverse effect of infectious diseases on temperatures in those with psychiatric disorders needs to be remembered (45). Psychologically vulnerable subjects were found to be more severely ill, showed greater mood changes in prodromal period, had a more prolonged febrile course in time, and occasionally had mood changes extending into convalescence. We recently had a patient with protracted CMV infection who developed significant feelings of hostility and reported aberrant thoughts of violent behavior in

the second month of illness. Hence, persons with borderline personality disorders may have prolonged fever and abnormal behavior patterns with fever (46).

Rules in approach to FUO (47): Observe patterns of clinical illness - Are there any findings that might fit a systemic pattern? Pay attention to pain at any site: teeth, previous operative site. If fever persists after negative scans or biopsies, repeat tests, especially if weight loss, anorexia or objective findings present. If unmarried male, obtain HTLV III (not cause of fever), CMV, EBV and toxoplasma titers. Can have non-specific findings before immunodeficiency leads to a specific infection. Check medication record. Be patient - Eventually, you'll find the answer, even if there is no answer.

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All the residents who've made ID rotation so much fun.

Becky Rendon and Susan Kennedy, who made the preparation of this tome easier.

Ode to FUO

Fever, oh fever,
From whence doth thy come?
Where are thy roots,
Oh, mysterious one?

O'er thy origin, we ponder
As the hour doth pass,
And test after test
As we seek it at last!

The place of thy birth,
Where thou was begot,
Alas, . . . thou hast gone,
And we findeth it not.

H.C. Gibson

Winner of 1985 VA-IDS Invitational FUO Poetry Contest
(Many were invited, but few entered)

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