FUO REVISITED*

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LA JOLLA AND SEATTLE

In 1961 Beeson and I published an analysis of 100 patients with FUO (1). These patients had been studied in New Haven during the 1950s and the study differed from previous ones because it was prospective and included a follow-up on all patients. The study also employed strict criteria (Table 1) which excluded most patients in whom the diagnosis of fever was obvious.

During the ensuing 20 years the practice of medicine changed radically. In particular, diagnostic sophistication improved remarkably. It seemed worthwhile, therefore, to repeat this study in the 1970s, some 20 years after the first one was conducted. The second study was conducted in Seattle, Washington and 105 patients were analyzed. The same criteria for inclusion were used. The brief overview that follows presents the results of the second study, and compares them with the first (2).

Diagnosis of FUO

Table 2 summarizes the categories of disease causing FUO in both series and points out the increasing prevalence of neoplasms, fewer infections, a fall-off in connective tissue diseases, and a remarkably similar prevalence of undiagnosed cases of FUO.

Table 3 enumerates the major diseases in the first series that were markedly decreased in the second, and Table 4 shows the diseases prominent in the 1980 analysis that were not known to cause FUO in 1960.

There were as many abscesses in this series as in the previous one, (Table 5) but fewer were found in the right upper quadrant. The most important point concerning abscesses is that the only patients with infections who died had abscesses and in every instance their lives could have been saved had the diagnosis been made.

In the first FUO series tuberculosis was the most common infection causing FUO (Table 6). However, tuberculosis had decreased markedly in incidence by the 1970's. The disease continued to be dominant in

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TABLE 1
Criteria for FUO

- Temperature >101°F
- Duration ≥3 weeks
- One week intelligent investigation

TABLE 2
Diagnostic Categories

	1980 Series		1960 Series	
	#	%	#	%
Infections	32	30	36	36
Neoplasms	33	31	19	19
Collagen Diseases	9	9	15	15
Granulomas	8	8	4	4
Miscellaneous	10	10	19	19
No Dx	13	12	7	7
Total	105	100	100	100

TABLE 3
Diseases Prominent in 1960 but sharply Decreased or Absent in 1980

Tuberculosis
SBE
Rheumatic Fever
SLE
Familial Mediterranean Fever

TABLE 4
Diseases Not Seen or Rare in 1960 but Prominent in 1980

CMV
Osteomyelitis
Sinusitis
Malignant Histiocytosis
Still's Disease
Crohn's Disease
Hematomas

blacks. The diagnosis could have been made much earlier if localizing signs and symptoms had been followed more vigorously. In contrast to the earlier series, these patients did remarkably well with chemotherapy, probably due to the advent of rifampin.

Four patients had cytomegalovirus infections (Table 7) a disease that was unknown in 1960. These patients typically had non-specific constitutional symptoms, "shotty" generalized lymphadenopathy and modest hepatosplenomegaly, and they were characteristically not ill. Watchful

TABLE 5
Abscesses

	Number of Cases	
	Second Series	First Series
Abdominal abscesses (including liver and biliary tract):		
Subphrenic	3	2
Splenic	2	0
Diverticular	2	0
Liver and biliary tract	3	7
Pelvic	1	2
Total	11	11

TABLE 6
Mycobacterial Infections

5 patients (11 previous series)
4 Black
Dx node Bx (3); marrow; tissue
4 Extrapulmonary
1 Atypical AFB
Steroids in 2 miliary cases
Good response to chemotherapy

TABLE 7
CMV Infections

4 Patients (none previous series)
Fever; Constitutional Sx
Shotty nodes
No anemia; atypical lymphs
Hepatitis (SGOT, SGPT 2-3x nl)
3 Acquired; 1 Post-perfusion
All recovered
FUO Work-up unnecessary

waiting for serologic results could have avoided a long and sometimes painful FUO workup.

Other causes of infection included urinary tract infections which were always associated with obstruction; sinusitis, in one instance caused by blockage of the maxillary ostium with a nasogastric tube; and vertebral osteomyelitis following urinary tract infection.

Table 8 depicts the cancers that caused FUOs: the predominance of lymphomas is noteworthy. Patients with Hodgkin's Disease (Table 9) usually had retroperitoneal disease which was diagnosed by laparotomy or biopsy. The diagnosis was important because these patients did very well with treatment.

In contrast, patients with FUO due to non-Hodgkin's lymphoma did very poorly (Table 10). The diagnosis was usually made by biopsy and in several instances the histology of lymphatic tissue was difficult to interpret. Survival after diagnosis was disappointingly short.

We became acquainted with a new disease, malignant histiocytosis (Table 11), which was characterized by fever, wasting, generalized lymphadenopathy, and enlargement of the liver and spleen. This disease was rapidly progressive with very high fever, weight loss and depressed counts of at least one blood cell line. We also saw one patient with angioimmu-

TABLE 8
Neoplastic Diseases

	Number of Cases	
	Second Series	First Series
Lymphoma, leukemia and related malignancies:		
Non-Hodgkin's lymphoma	7	4
Leukemia	5	2
Hodgkin's Disease	4	2
Other reticuloendothelial malignancies	4	0
Other lymphocytic malignancies	2	0
Subtotal	22	8
Solid tumors	11	9
No histologic diagnosis	0	2
Total	33	19

TABLE 9
Hodgkin's Disease

4 patients (2 previous series)
Fever; night sweats, anorexia, weight loss
Lymphadenopathy (2)
Anemia (4); ESR > 100 (2)
Intraabdominal
Clues: IVP, Lymphangiopathy, Liver Scan
Dx: Laparotomy (2); Biopsy (2)
Long survival

TABLE 10
Non-Hodgkin's Lymphoma

7 Patients (4 previous series)
Sx—nonspecific
Hepatomegaly (6); Bone pain (1)
Anemia; wbc ↑ or N
Dx = Biopsy Node (3); marrow (2); lap (2)
Outcome poor

TABLE 11
Malignant Histiocytosis

4 patients
Rapidly progressive
High fevers (40°C–41.4°C)
Weight loss
Penia (rbc, wbc, platelets)
Marrow involvement and nodes, liver, spleen, lung
Histology difficult

TABLE 12
Leukemias

5 patients
No blasts initially
Anemia, cytopenia
Maturation arrest
Preleukemia 3/5

TABLE 13
Collagen Diseases

	Number of Cases	
	Second Series	First Series
Still's disease	4	2
Polyarteritis nodosa	2	0
Giant cell arteritis	1	2
Panaortitis and arteritis	1	0
Rheumatic fever	1	6
Systemic lupus erythematosus	0	5
Total	9	15

noblastic lymphadenopathy and one with lymphomatoid granulomatosis.

Table 12 summarizes the major features of our patients with leukemia. All had a preleukemic picture without classical blast cells in the blood or bone marrow when they first presented.

All solid tumors had metastasized to the liver and it should not be surprising that the duration of these patients' illnesses was remarkably short.

There were fewer patients with collagen diseases (Table 13) probably because patients with lupus erythematosus were culled out by means of immunologic tests and because rheumatic fever seems to be disappearing. This left us with a variety of arteritides and juvenile rheumatoid arthritis. Table 14 shows the main characteristics of this entity which was seen in young adults with high spiking fevers, intense myalgias and arthralgias, but rarely with frank arthritis. Three of 4 patients had white counts

between 20,000 and 30,000. The diagnosis was difficult because physicians were slow to consider it, and because the systemic manifestations such as the rash and fever tended to overshadow the arthritis. These patients all did well with antiinflammatory therapy.

Table 15 shows the three most common granulomatous diseases: Crohn's disease, erythema nodosum and granulomatous hepatitis. This illness was detected by liver biopsy and resolved with antiinflammatory therapy which had to be administered for a long period of time (Table 16).

Miscellaneous causes of FUO are listed in Table 17. Noteworthy was the abssence of pulmonary emboli and Familial Mediterranean Fever in this series. Cryptic hematomas need to be considered in the differential diagnosis of FUO. And, of course, there were our familiar friends with factitious fever (3).

Finally, there was a group of patients that remained undiagnosed (Table 18). In several the illness subsided spontaneously, and some responded to antibiotics, while others required supression of fever with

TABLE 14
Juvenile Rheumatoid Arthritis

4 young adults
High spiking fever; arthralgias; myalgias
WBC 20–30,000
Respond to: ASA, indomethacin, steroids

TABLE 15
Granulomatous Diseases

	Number of Cases	
	Second Series	First Series
Granulomatous hepatitis	4	2
Crohn's disease	2	0
Sarcoidosis, erythemanodosum	2	2
Total	8	4

TABLE 16
Granulomatous Hepatitis

4 Patients
Dx: Liver Bx
Hepatomegaly + abnormal LFT's
Hx of Penicillin
Non-caseating granulomas
Response to anti-inflammatory drugs
Complete recovery

TABLE 17
Miscellaneous Causes of FUO

	Number of Cases	
	Second Series	First Series
Hematomas	3	0
Pulmonary embolus	1	3
Familial Mediterranean Fever	1	0
Myxoma	1	0
Non-specific pericarditis	1	2
Other	0	6
Periodic Fever	0	5
Factitious Fever	3	3
Total	10	19

TABLE 18
Undiagnosed FUO

Resolved	
Viral-like syndrome	4
With antibiotics	2
S̄ Rx	1
Recurrent, steroid responsive	
Non-specific hepatitis	2
Elderly, fever, anemia, ↑ ESR	2
? Vasculitis	1
? Still's Disease	1

TABLE 19
Outcome of FUO

Died	42
2° to FUO	35
Survived	63
Benefit from Rx	42
Cure	27
Improved s̄ Rx	21
Dx only at autopsy	8

steroids. These patients probably had arteritis or a geriatric form of Still's Disease.

Outcome of FUO

Follow-up data were obtained and are depicted in Table 19. 42 patients, mainly elderly people with cancer, died. Thirty-five of these deaths were due to FUO. Of the 63 who survived, 42 benefited from medical or surgical therapy and 27 were cured. The remaining 21 improved without therapy. In all, 8 patients were diagnosed at autopsy, three of whom could have

been saved. These results are similar to the previous series where nine patients were autopsied and two had reversible disease (1).

Diagnostic Modalities

Of the various diagnostic modalities, biopsies and laparotomies remain the single most valuable diagnostic modality (Table 20). Bone marrow biopsy was the most valuable examination when tissue was sampled blindly. Liver biopsy yielded less information than had been our experience previously. It was of greatest value in granulomatous hepatitis. Biopsies of other tissues were particularly valuable when there were clues to lead to the proper area. Laparotomy provided the diagnosis in nearly half the cases in which it was done, and was most valuable in solid tumors and abscesses. It was not diagnostic in 8 patients and normal in 13. In the absence of specific clues, laparotomy should not be performed.

Table 21 shows the innumerable tests to which these patients were

TABLE 20
Biopsies and Laparatomy

Marrow—valuable blind
Liver—Granulomatous hepatitis
Other tissues—Productive with other clues
Laparotomy—
19/40—Solid tumors, abscesses
8—Non diagnostic
13—Normal

TABLE 21
Value of Laboratory and Other Diagnostic Tests

Hematology—not specific
Chemistries—worthless
Immunology—not helpful
Microbiology—
Abscesses—helpful
Mycobacterial infections—helpful
Blood cultures—wasteful
Serology—CMV only
Skin tests—rarely helpful
X-rays—
Chest—helpful
Old films—helpful
Others—rarely helpful
Scans—
Liver Scan—useful
Gallium—misleading
Ultrasonography—improving
CT Scans—promising

subjected. Abnormalities were present in most, but were not specific. Routine chemistries were worthless and liver function tests were nonspecifically abnormal. Immunologic tests were of no help. This may be due to the fact that they called out patients with immune diseases before they could develop FUOs. Microbiologic tests were helpful in abscesses and mycobacterial infections. Blood cultures were very wasteful. Although a third of our patients had more than 20 blood cultures, they detected no bacteremias. Serologic and skin tests were rarely helpful. Among x-rays the chest film was the most valuable, followed closely by a review of old films which was often very helpful. In contrast, most other films did not provide useful information. Among the scans, the technetium liver scan was the most useful. In contrast, gallium scans were plagued by false-positives and false-negatives. Relatively few patients in this series had ultrasonograms and CT scans. I would classify these as promising.

Concluding Remarks

I have had a love affair with FUO for 30 years. It is one of the relatively few syndromes in internal medicine that not only poses an enormous intellectual challenge, but is a condition where the physician's skill can really help the patient. I hope you agree that my affection is not misplaced.

REFERENCES

1. Petersdorf RG, Beeson PB: Fever of unexplained origin: report of 100 cases. *Medicine* 1961; **40:** 1-30.
2. Larson EB, Featherstone HJ, Petersdorf RG: Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970-1980. *Medicine* 1982; **61:** 269-292.
3. Aduan RP, Fauci AS, Dale DC, et al: Factitious fever and self-induced infection. *Ann Intern Med* 1979; **90:** 230.

DISCUSSION

Williams (Davis): Bob, you've often been considered a jewel as well as a jeweler in academic medicine, the latter by virtue of your tendency to deliver pearls—clinical pearls, that is—and I wonder if you would comment on whether there are any clinical pearls in the examination of these patients that help one avoid the lengthy workup? I'm specifically interested in whether the form or shape of the fever curve is a useful clinical observation that might help in the diagnosis.

Petersdorf: No, not really, Hibbard. Many years ago, when I was a young man at Hopkins, I inspected several hundred charts to see whether or not the inversion of the fever curve called "typus inversus" was of any diagnostic usefulness. It was not, and over the years I have found that while one can have grandiose abstruse discussions about fever curves, they don't help a great deal. Now, let me tell you what I have found most useful as a Visiting Professor. I have been presented an awful lot of these patients over the years, and usually by the time they get to me, every test that I could possibly think of has been

done and every differential diagnosis has been mentioned. And the only useful function that I perform is to take a look at the patient, to examine the patient, and to say, "for heaven's sake, don't operate on this patient" because, half the time, the patient is being wheeled to the operating room, the surgeon is on call and they are going to do the surgery right then and there. I say, "look, I don't know what this patient has, but that patient is getting better. Don't cut on him." And usually the people are persuaded that they ought not to cut and they don't, and that has been my single most useful function. And now that we are all so cost-conscious, I can brag that my efforts have reduced the hospital bill to some extent. But it is terribly important to take a close look at the patient and not to go ahead with an FUO workup when you have a patient who is getting better. That is the most important issue in FUO. Everybody reads everything and does every test and after all tests have been done and the diagnosis is not forthcoming, they drop the knife. Most of the time, the knife does not need to be dropped and that is the only pearl that I can leave with you today.

Wolff (Boston): Bob, that is a beautiful presentation. As you know, I share your love for FUOs and have for a number of years been seeing these patients. At Bethesda, we studied 347 patients who had had fever for an average of one year. They represented the 12% that remained with the diagnosis of FUO in your series. Everyone of our patients had been worked up at another institution and had come to us with a diagnosis of FUO. After our evaluation, fully one quarter of them didn't have fever—they were what many physicians call "low grade FUO" or functional or hyperthermic fever; in 20% of our patients, we were unable to make a diagnosis. Fully 9% of our patients had factitious disease and these have been reported by us a couple of years ago in the *Annals*. Since I've been in Boston 10% of all the FUOs referred to us are factitious, and I don't know whether the physicians suspect that when they refer them or our suspicions are so high. Eight percent of our patients had granulomatous hepatitis. As you know, we reported the latter group first at this meeting in 1971. Despite the fact that the average length of illness was one year, fully 7% of our patients had neoplastic disease, 6% were adults with Still's Disease and 6% had infections as a cause of their FUO. These were the unusual kinds of infections that you might see hidden in bone or other places that presented as FUOs. Four percent had collagen-vascular diseases—the same types that you've reported—and 3% had familial Mediterranean Fever and the only reason that 3% is up there is that each of these individuals came from Northern European extraction and physicians were unwilling to make that diagnosis in these particular ethnic groups.

Petersdorf: I want Dr. Wolff to know how grateful all of us are to him for one: describing some of the diseases which we've talked about; and, secondly, when he was at the NIH for accepting the disgruntled patients with FUO for whom we didn't have an answer. A fringe benefit was that at NIH, it didn't cost anything. But now that Dr. Wolff is at Tufts it costs a lot. Although I am glad that he is getting 10% of the patients in the Boston area (I used to refer him all my patients in the Boston area with FUO) they sometimes complained to me about their bills.

Horwitz (Philadelphia): I'd like to just report one case that occured in 1847. It was an FUO and the pre-autopsy diagnosis was that of having been hit by a tennis ball—tennis balls were very hard at that time. The patient was Frederick Prince of Wales, father of George III and the autopsy report read as follows: "Upon being split open, an impostume was found on the left hand side" (I had to look up to see what "impostume" was. It means "abscess".) If Frederick had received proper diagnostic and therapeutic care, and lived, he would have been King instead of George III, his son, and we would still be part of the Empire. I also want to make one other remark, and that is that your Willie Sutton Syndrome, which I didn't know that you'd invented—otherwise I'd have quoted you on it—is in the first paragraph of a book that we put out about 7 years ago. Thank you very much, it was an informative presentation.

Clifton (Iowa): Bob, would you give us your opinion of the current usefulness of exploratory laparotomy, now that we have CAT scans and so forth. I ask that because I believe laparotomy through the years has been a useful diagnostic procedure for patients with prolonged FUO, especially if their condition deteriorates. The housestaff now argue vehemently against it. I recently took care of a patient with FUO in whom all scans were negative. I prevailed upon the surgeon to operate and, buried deep in the left lobe of the liver, posteriorly, was an abscess which was drained and the patient immediately got well.

Petersdorf: This case makes the point, I think, that there has to be a clue. The clue may be that, in this case, all the scans were negative. I don't know what the technical quality of the scans was, but I suspect that the patient still had evidence of intra-abdominal sepsis. The patient probably had leukocytosis, or may have had some pain in the shoulder. You didn't describe this case, so I don't know. All I am saying is, that if there are absolutely no clues, you ought not to operate. There is one additional point that we should make, and that is that sometimes we miss the clues and that the computer or we, our cerebrums, that is, are not good enough to pick them up. Finally, if an old-time clinician like you is sufficiently confident that there is something in the belly, even if you don't have a clue, you should follow your clinical judgement. All I am saying is that those 13 patients in our series in whom laparotomy was normal and the other 8 in whom it did not show anything did not need to be operated upon. So my view about laparotomy is that it should be done very carefully and very thougthfully and that in this instance, you, being a fine clinician, are better than your scans.

Kern (Denver): Bob, in view of the excellence of CT Scans and ultrasound today in making the diagnosis of intra-abdominal abscess, I'd be curious to know the location of the abscess in the three patients in whom it was missed.

Petersdorf: Two of them were in the right upper quadrant. One was in the porta hepatis and was missed at one operation; the patient was operated upon and the abscess was missed. The second abscess was a liver abscess and the third was in the spleen.