FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

ROBERT G. PETERSDORF* AND PAUL B. BEESON

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

TABLE OF CONTENTS

Introduction 1
Diagnostic categories 2
Infections 3
Tuberculosis 3
Biliary tract and liver 6
Bacterial endocarditis 6
Abdominal abscesses 7
Pyelonephritis 8
Miscellaneous bacterial infections 8
Psittacosis 9
Malaria 10
Neoplastic diseases 10
Disseminated carcinoma 10
Localized tumors 12
Lymphomas and leukemia 12
Collagen diseases 13
Rheumatic fever 13
Systemic lupus erythematosus 14
Unclassified collagen disease 14
Pulmonary embolization 15
Hypersensitivity states 16
Non-specific pericarditis 17
Sarcoidosis 17
Cranial arteritis 18
Periodic disease 19
Miscellaneous diseases 20
Weber-Christian disease 20
Thyroiditis 20
Ruptured spleen 21
Myelofibrosis 21
Factitious fever 21
No diagnosis established 22
Diagnosis in fever of unknown origin 23
Prognosis in fever of unknown origin 26
Concluding remarks 26

INTRODUCTION

In 1868 Wunderlich, a German clinician, published in monograph form a convincing demonstration of the value of measuring the body temperature in various diseases. This work was soon translated into other languages (1), and the practice of making regular measurements of body temperature quickly became standard throughout the world. Thus the thermometer became the first instrument of precision to be used in medical practice. Long before Wunderlich, of course, physicians had known that illness was sometimes manifested by increased body warmth: in fact the word "Fever" came to be used to designate a certain form or forms of illness. Benjamin Rush maintained that there was "only one fever," but by the early part of the nineteenth century clinicians were able to distinguish between some of them, such as typhoid and typhus fevers, purely on clinical grounds. The introduction of clinical thermometry happened to come at the same time as the discoveries of Pasteur and the beginning of the Golden Age of Bacteriology; soon, therefore, it was no longer acceptable to say that a patient was suffering from 'a fever': the challenge was to determine the cause of that fever. It was also recognized that although infectious processes were the commonest causes of fever, other kinds of disease could also affect temperature regulation, and that a great variety of causes required consideration in the differential diagnosis of febrile illness. This became one of the main fields in differential diagnosis, and many of the great clinicians of the first half of the twentieth century, such as Horder and Libman, owed their reputations in some part to successes in diagnosis of febrile disease.

Fever of unknown origin (F.U.O.) is a common clinical problem, encountered frequently in nearly all branches of practice. Fortunately the cause is oftenest an acute infection, which soon becomes evident and responds to treatment, or runs its course. In the present article we are not concerned with such short-term problems, but are restricting the discussion to cases of prolonged febrile illness of obscure cause. This is likely to be a source of perplexity and frustration to the physician, and for the patient the discomforts of illness are compounded by the anxiety of uncertainty. These unhappy victims understandably tend to seek additional medical

* Present address: Dept. of Medicine, University of Washington and King County Hospital, Seattle.

opinions, and may wander from hospital to hospital, repeatedly enduring the same questions, the same examinations, the same laboratory tests. The fact to be accepted at the outset of a discussion of this problem is that there are diseases capable of provoking high fever for weeks or months, or even years, without progressing to a stage where the true nature of the malady reveals itself, and for which we have no accurate methods of diagnosis.

Much has been written and said about the diagnosis of prolonged febrile illness. We do not propose here to attempt a detailed review of previous discussions, other than to note that they show with remarkable clarity the great shifts which are constantly taking place in medical practice. For example, the well known article written by Hamman and Wainwright in 1936 (2), which reports on 90 cases of prolonged febrile illness studied at the Johns Hopkins Hospital, includes 11 instances of fever due to syphilis, and nearly all of the discussion is devoted to infectious diseases. That discussion does not mention by name the two present-day differential diagnostic favorites, periarteritis nodosa and systemic lupus erythematosus.

Previous writings on fever of unexplained origin have almost invariably depended upon the method of retrospective analysis for the collection of case material. That is to say, the cases were selected either by reliance on memory or by culling them from the hospital records according to diagnosis at the time of discharge. Obvious disadvantages are that cases assembled simply on the basis of recollection may present a distorted picture of the total problem; and that restricting the material to cases in which not even a tentative diagnosis had been achieved by the time of discharge from the hospital is certain to eliminate many in which there may have been long periods of uncertainty before a diagnosis could be made.

In an attempt to avoid some of the drawbacks just cited, and to obtain a present-day sampling of the problem of unexplained fever in adults, we undertook the present study in 1952. It was decided simply to note cases of prolonged unexplained fever satisfying certain criteria, at the time of their occurrence, with the intention of further study by follow-up methods at a later date. The criteria selected were: *Illness of more than three weeks' duration.* This tended to eliminate the acute self-limited infectious diseases. In some reported series such cases have comprised as much as half of the case material. *Fever higher than 101°F on several occasions.* This eliminated the entity of 'habitual hyperthermia' (3). *Diagnosis uncertain after one week of study in hospital.* This time interval was selected as that which allows completion of the usual laboratory studies made initially in attempts to identify the cause of a febrile illness, examples being bacteriologic and serologic tests, radiologic examinanations, skin tests, etc.

In 1957, when there were more than 126 cases on the list, the period of collection was terminated, and the follow-up investigation was begun. Our community is well suited to this type of study, because of its size and the stability of its population. Nevertheless some of the patients could not be traced. Furthermore, in reviewing the records it seemed reasonably certain that some of the febrile illnesses listed had represented combinations of such common entities as urinary tract infection and thrombophlebitis; accordingly these were eliminated. It was convenient, then, to base the analysis on just 100 cases, in all of which satisfactory follow-up information was available. We are aware of some bias in the final selections, and do not wish to imply that the statistical information to be presented has more than a very general significance; nevertheless the relative frequencies in the various categories are thought to give a rough picture of the probabilities in cases of fever of unexplained origin in the United States, at the mid-point of the twentieth century.

DIAGNOSTIC CATEGORIES OF THE 100 CASES

The diagnostic categories into which we finally placed the 100 cases are shown in Table I, arranged in order of frequency. It will be seen that in 93 of them a reasonably certain diagnosis was eventually possible.

The 7 cases in which not even a satisfactory tentative diagnosis could be made despite follow-up information represent 6 instances where the patients appear to have made complete recoveries. Many possibilities suggest themselves. Some of the patients may now only be in periods of remission during the long courses of diseases such as systemic lupus erythematosus. Some may have been suffering from indolent infections, e.g. tuberculosis, myocsis, toxoplasmosis, wherein host defense mechanisms finally gained the upper hand. Hypersensitivity reactions may have ter-

minated. The disease called cranial arteritis tends to run a long course and then to subside; it would not be recognizable in the absence of involvement of a superficial artery or of sudden visual impairment. Whatever the nature of the diseases in these subjects, they comprise a sizeable portion of any series of cases of perplexing fever.

Among the 93 cases in which a reasonably certain diagnosis was eventually made we had not anticipated that more than one-third would prove to be examples of infectious disease. On the other hand we had predicted that the neoplastic and collagen groups would be larger. Five cases of periodic disease are undoubtedly an incorrect indication of the true frequency of this entity, since every one of these patients was referred to us because of our special interest in problems of unexplained febrile disease; however, it must be pointed out that patients with this disease are likely to consult many physicians and to be studied in several hospitals, because of the very long course of the disorder.

INFECTIONS

Tuberculosis

Despite many statements to the contrary, tuberculosis is still a common disease. It was the cause of fever in 11 of our patients, i.e. nearly one-third of cases due to infection. In general, these patients were younger than those with fever due to suppurative disease, and 5 of the 11 were Negroes, which stands in contrast to the racial distribution in the other categories, only 9 of the 89 being Negroes. Detailed information concerning the symptoms, signs and laboratory data of these patients is summarized in Table II.

In two patients (cases 1 and 2) the process was principally confined to the lung, although a transient pericardial rub occurred in one. Failure to establish the diagnosis earlier was attributable to the late appearance of an infiltrate in one case and to the initially negative tuberculin test in the other.

The remainder of the 11 patients had widespread tuberculosis and presented a variety of clinical pictures. For example, two (cases 3 and 4) presented with fever and hilar lymphadenopathy. Both developed pulmonary infiltrates while in the hospital. In both patients liver biopsy revealed granulomata suggestive of tuberculosis. It is likely, however, that the primary focus of infection was in the lungs, since mild pleurisy was the first symptom in one patient and acid-fast

TABLE I

Diagnostic Categories of the 100 Cases

Category	Number of Cases	
Infections		
Tuberculosis	11	
Liver and biliary tract infections	7	
Bacterial endocarditis	5	
Abdominal abscess	4	
Pyelonephritis	3	
Psittacosis	2	
Brucellosis	1	
Cirrhosis with E. coli bacteremia	1	
Gonococcal arthritis	1	
Malaria	1	
Total		36
Neoplastic diseases		
Disseminated carcinomatosis	7	
Localized tumor	2	
Lymphomas and leukemias	8	
No histologic diagnosis made	2	
		19
Collagen disease		
Rheumatic fever	6	
Systemic lupus erythematosus	5	
Unclassified	2	
		13
Pulmonary embolization		
Following myocardial infarction	1	
Endocardial fibroelastosis	1	
Thrombophlebitis migrans	1	
		3
Benign non-specific pericarditis		2
Sarcoidosis		2
Hypersensitivity states		
Granulomatous hepatitis	2	
Erythema multiforme	1	
Drug fever (dilantin)	1	
		4
Cranial arteritis		2
Periodic disease		5
Miscellaneous diseases		
Weber-Christian disease	1	
Thyroiditis	1	
Rupture of the spleen and pancreatitis	1	
Myelofibrosis	1	
		4
Factitious fever		3
No diagnosis made		7
Total		100

TABLE II

Clinical and Laboratory Data in 11 Patients with Tuberculosis

Case	Age	Race	Sex	Diagnosis	Symptoms	Signs	Fever		Laboratory Data					Clues to Diagnosis	Method of Diagnosis	Outcome
							Height	Duration (mos.)	Anemia	WBC	Diff.	PPD	Other			
1	25	N	F	Pulmonary tuberculosis, ?pericarditis	Fever, chills, anorexia, substernal pains	?Pericardial rub	102	2	+	Incr.	N	+		Developed pulmonary infiltrate	Gastric washing +	Improved
2	48	W	M	Pulmonary tuberculosis; silicosis	Arthralgia	Swelling fingers	104	2	+	N	N	0 to +		Conversion PPD; silicosis	Sputum +	Died
3	43	N	M	Pulmonary tuberculosis with dissemination	Chills, fever, sweats, pleurisy, cough	None	102	3	0	N	N	+		Hilar adenopathy, ?perihilar infiltrate, appearance nodular infiltrate	Liver biopsy, response to treatment	Improved
4	45	N	M	Pulmonary tuberculosis with dissemination	Malaise, fever	None	105	2	+	N	N	+		Hilar adenopathy, developed infiltrate	Liver biopsy, + sputum	Improved
5	67	W	M	Primary hepatic tuberculosis	Weight loss	Weakness, disorientation, hepatomegaly	104	1½	+	N	10% monos	0	Alk. p'tase 75 B.U.	Hepatomegaly	Liver and lymph node biopsy	Died
6	63	W	F	Primary hepatic tuberculosis	Fever	Rales	103	4	+	Incr.	N	+		?History tuberculosis	Laparotomy	Improved
7	30	W	F	Tuberculous meningitis with dissemination	Fever	Pregnant	104	1½	+	Incr.	Shift, left	0		Developed meningitis; miliary infiltrate	+ urine culture, response to treatment	Improved
8	66	N	M	Miliary tuberculosis	Weakness	Cachexia, fundal exudates	106	1½	+	N	25% monos	0		Fundal exudates	Autopsy	Died
9	46	W	M	Tuberculous pericarditis with dissemination	Fatigue, weight loss	Cachexia, generalized lymphadenopathy	103	2	0	N	N	+		Pericardial rub appeared	Liver and lymph node biopsy, sputum +, urine +	Improved
10	40	N	M	Tuberculous pericarditis	Fever	Heart enlarged, pericardial rub	103	3	+	N	N	+		Bloody pericardial fluid	Response to treatment	Improved
11	57	W	F	Tuberculosis of adrenals	Weakness	Hyperpigmented	103	2	+	N	6% eos	+	Na 129 K 6 NPN 49 ACTH test +	Calcified adrenals, history vertebral tuberculosis	Response to treatment	Improved

Incr. = Increase, N = Normal, + = Positive, 0 = Negative.

bacilli were isolated from the sputum in the second. Chapman and Whorton, in their review of 63 patients with miliary tuberculosis, stress that systemic symptoms usually overshadow evidence of localized disease and also point out the difficulty in arriving at the diagnosis which was made antemortem in only one-sixth of their patients (4).

The most likely route of dissemination from the lungs of these patients is to the hilar lymph nodes and thoracic duct and thence into the blood. A number of tubercle bacilli lodge in the liver, which is almost always involved in miliary tuberculosis. Even when the disease has appeared clinically to be confined to the lungs, tuberculous foci are found in the liver in 80 per cent of patients at autopsy (5).

At times hematogenous dissemination seems principally to involve the liver. Examples of this are cases 5 and 6, which may be representative of a form of the disease which has been called primary miliary tuberculosis of the liver (6). Patients with obvious pulmonary tuberculosis and metastatic tubercles in the liver or generalized miliary disease are excluded from this group. Symptoms consist of malaise, weakness, lassitude, abdominal distention and a notable absence of respiratory symptoms. Positive physical findings are usually confined to hepatosplenomegaly and ascites; anemia, leukopenia and hyperglobulinemia have been noted often. The concept of hepatic tuberculosis is, we think, a useful one and early recognition of this form of the disease may be lifesaving.

In two patients (cases 7 and 8), dissemination of acid-fast bacilli was first manifested by pericarditis. In one the diagnosis was most elusive and even pericardial biopsy was negative but an impressive response to anti-tuberculous therapy on two occasions, with lysis of fever and diminution in heart size, were accepted as strong evidence of tuberculosis. Several authors have commented upon the difficulty in making the diagnosis of tuberculous pericarditis; in 34 of the 95 patients described by Harvey and Whitehill the diagnosis could not be established with certainty (7). In our second patient pericarditis did not become obvious until late in the course, at a time when organisms could be recovered from liver and lymph node biopsies as well as from sputum and urine.

Two patients (cases 9 and 10) had classical miliary tuberculosis culminating in tuberculous meningitis. In one a "snow-storm" appeared in the lungs simultaneously with symptoms and signs of meningeal involvement; she responded well to therapy. The other had three spinal fluid examinations, all with normal findings, and an unsuccessful therapeutic trial with isoniazid and PAS. At necropsy he was found to have typical lesions of miliary tuberculosis, including early meningitis. An important but unappreciated clue in this patient was the presence of fundal exudates, most probably choroidal tubercles. It is of interest that both of these patients failed to react to PPD skin tests.

The last patient in this group had the classical stigmata of Addison's disease by physical examination and laboratory tests. Clues to the diagnosis were a history of tuberculosis of the vertebrae 9 years previously and calcification of the adrenals by x-ray, considered by Sanford and Favour the best sign differentiating tuberculous and nontuberculous adrenal insufficiency (8). Fever is unusual in Addison's disease, and its presence should suggest the possibility of active tuberculosis, particularly when associated with leukocytosis, elevation in sedimentation rate and a positive tuberculin test.

Delays in arriving at the diagnosis in our patients were related for the most part to the late involvement of organs likely to provoke characteristic manifestations, namely lung, pericardium and meninges. In 2 instances the waiting period necessary for the results of cultures was the cause of delay. In general, however, systemic dissemination seemed to be the most important factor in late diagnosis, since in several instances tuberculosis was not even seriously considered until several weeks after onset of fever.

Despite the fact that the tuberculin test was negative in 3 of our patients, it remains an important diagnostic procedure. The result was positive in 8 of 11 patients, 6 of whom had widely disseminated disease.

Because hematogenous spread was the rule in this group of patients, liver biopsy was very helpful in diagnosis; in fact, in 3 patients evidence of the disease was first obtained by means of this procedure. Acid-fast bacilli were seen in 2 of the specimens and were cultured from other tissues or body fluids in all three. In another patient tubercles were found in the liver at laparotomy.

When the condition of the patient will not

allow liver biopsy to be done, or if this and other diagnostic maneuvers fail, a therapeutic trial with anti-tuberculous drugs is indicated. In one of our patients prompt response to isoniazid strongly implicated tuberculosis as the cause of the fever. In another (case 8), who ultimately expired, a more extended trial might have been lifesaving.

Acute Infections of the Biliary Tract and Liver

Another unexpected finding was the fact that the series included no less than 7 instances of suppurative infection of the liver and biliary tract. Two patients had large single liver abscesses of cryptogenic origin, and the other five had acute cholecystitis and cholangitis; two in the latter category had empyema of the gallbladder. The diagnosis was made at laparotomy in 4 of them, and at autopsy in 2. In the remaining case a gas-containing abscess of the liver was demonstrated radiographically; it apparently resolved during a prolonged course of antibiotic therapy. Six of these patients were males.

Clinically detectable icterus was noted in only 2 patients. Pain and tenderness in the right upper abdomen were not notable in any of them. The fevers in these patients tended to be exceptionally high; temperature elevations exceeded 103°F in 7 of the cases, and 6 of them had more than one shaking chill. All but 1 had an elevation in leukocyte count, and in 3 it was more than 20,000 per cu.mm. Needle biopsy of the liver was done in 4 of the 7 cases, and the evidence obtained was not very helpful, showing at most some evidence of cholangitis.

One factor contributing to the difficulties in diagnosis in this group is found in their ages. All were more than 50 years old, and 4 were more than 70. It is common clinical knowledge that manifestations of acute intra-abdominal disease may be comparatively mild in elderly patients, who often experience little pain, and exhibit no tenderness or muscle splinting. One of our patients, a man of 78, complained only of chills and feverishness. He was examined many times during a period of 3 weeks, since the tentative clinical diagnosis was probable neoplasm, nevertheless no abdominal mass or tenderness was detected. At laparotomy, however, he was found to have empyema of the gallbladder and a subhepatic abscess containing 70 ml. of pus. The frequent absence of tenderness or muscle splinting in elderly patients with biliary tract infection has been mentioned by Fisher and White (9).

Review of the histories of these patients has made us conclude that one must always give serious consideration to the advisability of exploratory laparotomy in a person with prolonged unexplained fever, especially when the subject is a male past 50 pears of age. Failure to discover a curable disease such as empyema of the gallbladder is inexcusable.

Bacterial Endocarditis

Bacterial endocaritis was the eventual diagnosis in 5 cases in the series. In one patient, a man of 58 years, the delay in diagnosis was attributable to a confident clinical impression that he had another disease, and to the fact that he did not have a heart murmur early in the course of his illness. This man was admitted because of a brief episode of aphasia, which, in retrospect, should have received more consideration, but at the time was looked upon merely as a coincidental minor cerebral vascular accident. Our major focus of attention in the early stage of his hospital course was a small pulmonary infiltrate, thought to be due to tuberculosis. However, during a three-week period of observation, although fever continued, the pulmonary shadow became less conspicuous, a murmur of aortic insufficiency became audible, and there was a widening of the pulse pressure. Blood cultures were finally obtained and revealed the presence of *Streptococcus viridans*. He made a good clinical response to penicillin therapy. The occurrence of bacterial endocarditis on the aortic valve in males past the age of 50, with development of a murmur during the course of the illness is a not too rare sequence of events (10).

In the other patients bacterial endocarditis was one of the diseases considered from the beginning of the period of clinical observation. Delay in establishing the diagnosis was attributable in two cases to negative blood cultures, that is to say, these patients had the abacteremic form of the disease. One of them died and the diagnosis was verified at autopsy. The other was a 26-year-old man with tetralogy of Fallot. After many blood cultures had failed to give growth he was given a 3-week course of penicillin and streptomycin, with no subsidence of his fever; however, when therapy was discontinued his temperature quickly returned to normal and he has remained well for several years. It was concluded that he probably had bacterial endocarditis, cured during the chemotherapy, but the beneficial effect of

antibiotic treatment was obscured by the development of a drug fever. In the remaining 2 cases delay in making the diagnosis was the result of courses of antibotic therapy given to the patients before admission to the hospital; consequently the first few blood cultures taken after admission to the hospital yielded no growth, and not until the antibiotic effect had worn off was bacteremia demonstrable.

Thus the diagnosis of bacterial endocarditis was truly 'missed' in only 1 of these cases, the first described. In the other 4 that diagnosis was under serious consideration from the beginning, but there was delay because of negative blood cultures. It should be pointed out, on the other hand, that bacterial endocarditis nearly always comes up for consideration in any case of prolonged unexplained fever. In fact, several of the other cases in this series were 'given the benefit of a trial' of chemotherapy for that disease. This seems impossible to avoid: the physician can never be certain that he is *not* dealing with an abacteremic case of bacterial endocarditis, and often feels compelled to try the effect of antibiotic therapy, fearful that he may be overlooking a possible curative treatment of an otherwise fatal disease.

Abdominal Abscesses

Four patients were eventually discovered to have deep-seated abscesses within the abdominal cavity. In two Negro females, the abscesses were in the pelvis. One, aged 32, entered the hospital for an elective surgical procedure, and was found to have a fever for which there was no obvious cause. She was transferred to the Medical Service, for investigation of the fever, and subjected to the usual battery of diagnostic tests, including chest x-ray, bacteriologic and serologic examinations, L.E. tests, etc. After three weeks of this a mass was discovered in her lower abdomen, and exploratory laparotomy was carried out. This revealed a large tubo-ovarian abscess, removal of which resulted in prompt cessation of the fever. Even after the nature of this illness was recognized the patient denied having had abdominal pain or menstrual abnormality; nevertheless, we feel that the correct diagnosis should have been made much earlier than it was. The case illustrated one of the weaknesses inherent in the increasing specialization of modern medical practice. The diagnostic study was in the hands of people whose thinking was more likely to turn in the direction of collagen diseases than such every-day entities as pelvic inflammatory disease.

The second patient, aged 57, had suffered fever and night sweats for 6 months, and had lost a considerable amount of weight. When admitted to the hospital her hemoglobin was 5.8 Gm. per 100 ml., and leukocyte count 22,000 per cu. mm. Her temperature rose as high as 103°F. Carcinoma of the gastrointestinal tract was strongly suspected, but radiographic studies, including barium enema were interpreted as showing normal patterns. Liver biopsy, agglutination tests, L.E. tests, etc., were not helpful. After one month she complained, for the first time, of abdominal pain. It was decided to carry out a laparotomy; this revealed the presence of a pelvic abscess, almost certainly originating from appendicitis many months previously. She made an excellent recovery.

The other two intra-abdominal abscesses occurred in males, and the causative bacteria belonged to the Salmonella group. One patient was a 70-year-old Negro, who had been ill for 2 weeks, with fever and chills, but who denied all other symptoms. In the past he had suffered some indigestion, and his physician had made a diagnosis of peptic ulcer. Examination revealed no abdominal tenderness, and no mass was detected; however, radiologic study of the upper gastrointestinal tract did show a large gastric ulcer, possibly malignant. Because of his high fever, many blood cultures were made, and eventually some of these yielded *S. choleraesuis*. Treatment with chloramphenicol caused some improvement, but there was a relapse at the end of the course of chemotherapy. It was then decided to go ahead with laparotomy, and this disclosed that the patient had suffered a perforation of a large benign gastric ulcer, with the formation of a large abscess in the lesser peritoneal sac. Partial gastrectomy was done, the abscess was drained, and chloramphenicol therapy was resumed. He made an excellent recovery.

The last patient in this group was 57 years of age, and gave a history of intermittent chills and fever for the preceding 10 months. Studies in another hospital had revealed hepatosplenomegaly, and liver biopsy had been interpreted as showing hemochromatosis, but the cause of the chills and fever had not been determined. In our hospital many blood cultures were negative, but eventually *S. montevideo* was recovered from cul-

ture of material aspirated from the bone marrow. Later the same organism was identified occasionally in blood cultures. Chloramphenicol therapy did not affect his fever. Laparotomy was carried out; the gallbladder appeared abnormal and was removed. Chloramphenicol treatment was continued, and his fever abated. He made a partial clinical recovery, but died one year later as a result of hemorrhage from esophageal varices. At autopsy he was found to have the remnant of a large abscess in the left subphrenic area. Presumably this focus of infection had been sterilized during the long course of chemotherapy.

An interesting clinical feature of the case just described is that there was an inversion of the usual temperature rhythm. For many weeks his highest daily elevation occurred in the early hours of the morning, whereas the lowest was in the afternoon. In our experience this is a surprisingly rare phenomenon. It has been said to characterize the fever of tuberculosis, but must be exceptional, and merely a consequence of the frequency of tuberculosis as a cause of long- continued fever.

Pyelonephritis

Coliform bacterial infection of the kidney was the disease of 3 patients in this series. They were females, aged 40, 60 and 71 years. None had symptoms of cystitis, and pyuria was absent, or scanty and intermittent. Urine cultures were negative in one, intermittently positive in the second, and consistently positive in the third.

The diagnostic clue in the oldest patient was detection of a tumor in the region of the left kidney after a two-month febrile illness. Intravenous pyelogram had been done elsewhere at the beginning of this illness, and interpreted as normal. However, retrograde pyelogram done after the finding of the 'tumor' showed a deformity of the renal pelvic outline, with a large opacity in the region of that kidney. The tentative preoperative diagnosis was hypernephroma. She was found, however, to have a chronically infected kidney and a large peri-nephric abscess, from which *E. coli* was recovered in pure culture. It is of interest to note that the mass, which consisted of kidney and its surrounding purulent mass, was thought to move freely with repiration, a characteristic not rare in perinephric abscesses (11). Extension of the suppuration to the perinephric space is, of course, uncommon in *E. coli* infection, and most likely to occur when there is complete ureteral obstruction. Calculi were not found in this patient, and the pyelographic findings were not consistent with complete ureteral obstruction.

The second patient was a 60-year-old woman with hypertension who gave a history of several episodes of pyelitis of pregnancy. Urine cultures revealed the presence of *E. coli*, but no pyuria was demonstrated, and she was thought at first merely to have asymptomatic bacteriuria. Antimicrobial therapy did not affect her fever. Many diagnostic tests were performed, searching for signs of a variety of kinds of illness. Intravenous pyelogram showed renal opacification on the right; therefore, it was decided to explore the region surgically. The right kidney was found to be a small, severely scarred organ, with some evidence of active bacterial infection. Nephrectomy was done, and her fever subsided, although urine cultures continued to yield *E. coli*.

The third patient, a woman of 40, had hypertensive heart disease and mild congestive heart failure. Intravenous pyelograms were interpreted as normal, and urine cultures never revealed large numbers of bacteria, although *E. coli* in quantities of borderline significance, i.e. 1000 to 5000 per ml., was present several times. Many blood cultures were made, but these gave no growth. Nevertheless because of unexplained fever and a heart murmur it was thought possible that she had bacterial endocarditis in an abacteremic phase. Accordingly she was given a course of penicillin and streptomycin. This had no effect on the fever. In view of the questionably significant urine cultures it was then decided to try the effect of a prolonged course of streptomycin and tetracycline. At the end of ten days of that therapy her fever subsided and the urine cultures became negative. The diagnosis of pyelonephritis was assumed to be the probable one, though not definitely established. Although the only example in the present series, this is not the only instance in which we have observed pyelonephritis to simulate bacterial endocarditis. This disease can simulate many other syndromes as recently discussed by Schreiner (12).

Miscellaneous Bacterial Infections

Brucellosis with hepatitis. Brucellosis is generally regarded as one of the 'classic' causes of pyrexia of unknown origin, hence the possibility

of this infection is nearly always brought up for consideration. Only one instance qualified for inclusion in this series of cases, and there the delay in diagnosis was due to the fact that the principal manifestations were those of liver disease. The patient worked in a meat packing house, and had been ill for 7 weeks before admission with fever, and weakness. A few days before admission to the hospital he noted that his urine was dark and that his eyes appeared yellow. On examination, in addition to the icterus there was noted considerable enlargement of the liver and spleen. Liver function tests indicated active parenchymatous disease. Liver biopsy was interpreted as showing a subacute hepatic necrosis and a granulomatous hepatitis, consistent with brucellosis (13). Agglutination reaction was strongly positive, and he improved rapidly following treatment with tetracycline and streptomycin. Reviewing this case it appears that failure to give sufficient thought to the patient's work, as well as preoccupation with other causes of hepatitis, were responsible for delayed recognition of an unusual form of brucellosis.

Gonococcal arthritis. A 49-year-old Negro man had been ill for 3 weeks before admission, with fever and a swollen knee. He denied symptoms of gonococcal urethritis and no evidence of that could be detected. During 4 weeks in the hospital other joints became swollen and painful, and his temperature rose as high as 104°F. Three years previously he had recovered from miliary tuberculosis. Diagnoses under consideration included recurrence of tuberculosis, as well as rheumatic fever and rheumatoid arthritis. At length fluid was aspirated from the knee, which, on examination by Gram stain, showed Gram-negative cocci; culture of the fluid, however, gave no growth. Complement fixation test for gonococcal infection was postive. The patient's signs and symptoms cleared gradually under treatment with penicillin and chloramphenicol, and he progressed to complete recovery. It seems reasonable to assume that this was a case of gonococcal arthritis.

Hepatic cirrhosis with E. coli bacteremia. Occasionally patients with Laennec's cirrhosis suffer acute febrile episodes associated with *E. coli* bacteremia (14, 15). One of our cases belongs in this category. He was 50 years of age, had been addicted to alcohol for many years, and had been told 12 years previously that he had cirrhosis. For 2 weeks prior to admission, and for 1 week afterward he had a febrile illness, with elevations as high as 104°F. Physical examination revealed hepatosplenomegaly and other signs of chronic liver disease, and liver function tests supported this. While in the hospital one blood culture was positive for *E. coli.* His febrile illness subsided without antibiotic therapy and he was permitted to return to his home. However, he suffered a relapse 1 week later, with elevations to 105°F. He was re-admitted, and blood cultures this time showed no growth; however, in view of the clinical picture and the previous demonstration of bacteremia, chloramphenicol treatment was instituted. The patient made rapid improvement. He died 14 months later in another hospital, following an intestinal resection for mesenteric thrombosis. Autopsy revealed only the presence of cirrhosis, and there was no clue to the original focus of the *E. coli* infection.

Episodes of coliform bacteremia in patients with severe liver disease have been recognized for a long time, but the paucity of literature about them suggests that they occur rarely. A recent report from Paris, however, tends to refute this and suggests that this is the most frequent kind of septicemia in cirrhotics. These authors report observation of 15 examples of this complication among 450 patients with cirrhosis (16). The curious thing about the episodes is that they often occur 'out of the blue,' without any indication of the existence of a primary focus of infection. The suggestion has been made that they occur as a result of the shunting of portal blood into the peripheral circulation because of portal hypertension. This is not wholly satisfying, because it has not yet been conclusively demonstrated that living bacteria frequently gain access to the portal circulation of man. The pathogenesis of these episodes is deserving of further study.

Psittacosis

Before giving further details of these two cases of psittacosis it seems worth while to emphasize the fact that infections by viruses rarely produce prolonged febrile illness. While it is true that lymphogranuloma venereum, trachoma and infectious hepatitis (if that is a viral infection) may be cited as viral infections in which there is chronic progression of the lesion, none of these is characterized by fever. For the most part, then, the clinician faced with a problem of long-term

unexplained febrile illness, can dismiss viral infections from primary consideration.

The only instances of infection by viruses which appear in this group of cases are 2 cases of psittacosis. They barely qualify for inclusion on the basis of illness of 3 weeks or slightly longer, with the diagnosis still uncertain at the end of one week's study in the hospital. In both cases it was clear that there was a pathologic lesion of the lung, but differentiation from primary atypical pneumonia, tuberculosis, mycosis, 'allergic pneumonitis' and other entities could not be made promptly.

The two cases of psittacosis occurred in females, aged 32 and 46. A history of contact with parakeets was later obtained in both patients. Their illnesses were characterized by fever and systemic manifestations with comparatively little cough and no expectoration. In each one of them a pulmonary infiltrate was demonstrated by x-ray during the third week of illness, and in one there were physical signs of consolidation. One patient developed a few macular lesions on the trunk somewhat resembling rose spots of typhoid fever. This has been noted before, and may indeed cause confusion with typhoid (17), in view of the fact that psittacosis may be manifested by fever, headache, abdominal distension, leukopenia and splenomegaly. The many diagnostic possibilities which may be suggested by cases of psittacosis have been discussed more recently by Seibert et al. (18). In both of our cases the diagnosis was established by rising titer of complement fixing antibodies for psittacosis virus. One of our cases made a good recovery after four weeks without specific therapy. The other improved during a course of penicillin treatment.

Malaria

A typical case of malaria qualified for admission to this series of cases, simply because the possibility was not considered at first. The patient was a 34-year-old man who, 7 months previous to onset of symptoms, had been engaged in entomological investigations in Panama. While there he had taken suppressive doses of chloroquin, but had had no antimalarial therapy since his return to Connecticut. His illness began with myalgia, headache and malaise, and fever to 101°F. A tentative diagnosis of infectious mononucleosis was made. After two weeks of febrile illness at home without improvement he was admitted to the hospital for study. Blood cultures, agglutination tests, radiological examinations, etc. revealed nothing of significance. Meanwhile his temperature rose as high as 105°. At length the significance of recent exposure to malaria was appreciated, and smears of the peripheral blood revealed *Plasmodium vivax*. He was cured by appropriate antimalarial therapy.

NEOPLASTIC DISEASES

Nineteen of the cases in this series had fever as a symptom of neoplastic disease. Eight of these were in the lymphoma-leukemia category; 11 were carcinoma or sarcoma.

Fever is a well known manifestation of neoplastic disease, and was given considerable attention in the writings of clinicians 50 years ago. Briggs reviewed 238 malignancies, and found fever, unrelated to other causes, to be present in 38 per cent (19). In the majority of his cases there were only occasional rises in temperature; only 7 of them had sustained fever. On the basis of these and other figures it would appear that roughly 3 per cent of patients with visceral carcinoma have fever as the presenting complaint.

Disseminated Carcinoma

In 7 patients there was wide dissemination of carcinoma, from primary foci in the pancreas, stomach, esophagus, carotid body, eye and bone. The organs most frequently affected by metastatic lesions were the liver and bones four times each, lungs three times and adrenals and abdominal lymph nodes in two cases each. Pyrexia could not be correlated with the locus of metastatic disease, and the pattern of dissemination in these febrile patients did not seem to differ from that which is usually observed (20).

Of note is the relative youth of these patients, 5 of whom were between 20 and 50 years of age. In general, the illnesses followed acute courses. In 6 patients symptoms had been present for less than 3 months, and consisted of fever, weakness, weight loss and pain, usually referable to a site of neoplastic infiltration.

Carcinoma of the pancreas. The two patients with this disease had remarkably similar illnesses. Both were middle-aged men; their symptoms were vague, and they maintained high fevers for many weeks. The correct diagnosis was eventually achieved by biopsy of an inguinal lymph node in one patient, and by

laparotomy in the other. Both of these men had leukemoid blood pictures; in one the leukocyte count remained in the vicinity of 60,000. The other's leukocyte count was about 30,000 and there was an eosinophilia of 25–30 per cent. Leukemoid reactions have been noted in a variety of malignant tumors (21). Isaacson and Rapaport called attention to eosinophilia in malignant disease, and described this phenomenon in 0.5 per cent of all malignancies at one hospital (22). Eosinophilia can be particularly confusing in patients with pyrexia of unknown etiology; for example, most of the attending physicians favored the diagnosis of periarteritis nodosa in our patient until the true nature of his disease was recognized.

The frequency of fever in all cases of carcinoma of the pancreas does not appear to be unusually high. In Bell's series fever was the presenting symptom in 6 of 466 cases (23). Cliffton points out that 50 per cent of patients with neoplastic infiltration in the ampulla of Vater have intermittent fever, but cites an incidence of only 2% in lesions elsewhere in the pancreas (24).

Carcinoma of the stomach. A 67-year-old woman complained of fever, with vague aches and pains, and was first thought to be suffering from psoriatic arthritis. Two months later x-rays of her skeleton revealed evidence of widespread metastatic malignancy, and the level of blood alkaline phosphatase was found to be 64 Bodansky units. Lymph node biopsy revealed an adenocarcinoma, which was later found to have originated in the stomach. This patient, then, had fever attributable to carcinoma of the stomach for 3 months. Gastric malignancy was thought by the older clinicians to be the prototype of a fever-producing tumor (19). This view was recently supported by Berlin and Porter (25), who reported 39 episodes of fever among 81 admissions for gastric malignancy, but in all but 6 of those the temperature elevations did not exceed 101°F. Hartmann analyzed the records of 271 patients with carcinoma of the stomach and found 8.8 per cent to have fever due to intercurrent infections and 7.7 per cent to have rhythmical "malaria-like" elevations in temperature occurring at intervals of 3–5 days. One of his patients became afebrile following gastrectomy (26).

Carcinoma of the esophagus. One of the worst diagnostic errors in this series occurred in the case of a 34-year-old Puerto Rican male who gave a history of vague epigastric pain for 5 months, and mild dysphagia for 2 months, with one minor episode of hematemesis. He had some fever, and one of the main possibilities under consideration was schistosomiasis. Radiographic examination of the upper gastrointestinal tract and colon were reported as normal. Esophagoscopy was planned, but not completed because of a hyperactive gag reflex. His fever subsided spontaneously and he was discharged, only to be re-admitted 3 weeks later because of chills and fever. At this time he underwent an extensive "F.U.O. work-up" including liver and lymph node biopsy, bone marrow examination and numerous culutres and x-rays. A tentative diagnosis of Hodgkin's disease was made, on the basis of low-grade eosinophilia, lymphocytic infiltration in the liver, and a rather classical Pel-Ebstein fever. When admitted for the third time, nausea, vomiting and dysphagia were the presenting complaints. Radiographic examination revealed a constricting lesion in the mid-esophagus, and the presence of carcinoma was established by biopsy. X-ray examination demonstrated metastases in the ribs and lungs and a broncho-esophageal fistula. Possibly the pyrexia was related to the communication between the bronchus and esophagus, and the several spontaneous defervescences may have followed intermittent drainage of infected material from the bronchial tree into the esophagus.

The lesson to be re-learned here is that dysphagia is by far the most common symptom of carcinoma of the esophagus and that failure to consider this possibility is the single most important cause for a delay in the diagnosis (27, 28).

Uncommon neoplasms. One patient had *malignant melanoma.* He had been febrile for 8 weeks and under study in the hospital for 2 weeks when the possible connection between the present illness and an ocular prosthesis inserted 8 years previously was brought up for consideration. The diagnosis was made by biopsy of the liver. Here we were chagrined at our failure to remember the old axiom about "the patient with a glass eye and a big liver." The interval between the removal of ocular melanoma and the appearance of metastases, usually in the liver, may be extremely long, a fact illustrated here

as well as by a number already in the medical literature (29).

One of the most unusual cases in this series involved a *fibrosarcoma of bone* in a young woman, who complained of fever and diffuse aches and pains. The initial impression was acute rheumatic fever, but discovery of a lesion in her rib 3 months after the onset of illness led to a biopsy which showed fibrosarcoma of bone. This tumor was first described by Steiner in 1944, and consists of numerous lesions widely-distributed in the reticuloendothelial and hematopoietic tissues of the marrow (30). It is thought to be of multicentric origin, and has some resemblance to multiple myeloma. The initial impression of acute rheumatic fever is reminiscent of the occational diagnosis of that disease in young patients with acute leukemia, as emphasized by Aisner and Hoxie (31).

Another unusual tumor was a *carcinoma of the carotid body,* with metastases. Many fruitless diagnostic procedures, including liver biopsy, were done in this patient, before a small mass in the neck, previously believed to be due to 'nonspecific lymphadenitis,' was excised and found to be a primary tumor of the carotid body.

Localized Tumors

In two patients localized neoplastic processes were the cause of fever. One of these was a 53-year-old woman who had daily elevations to 102°F for 18 months. She had been examined in several hospitals, had undergone innumerable radiographic studies, including intravenous pyelograms, cultures, and biopsies of bone marrow and liver, and had been subjected to therapeutic trials with a variety of drugs. There was clinical evidence of thyrotoxicosis, but propylthiouracil failed to affect the fever. A course of antituberculous therapy was likewise unsuccessful. Finally, repetition of the intravenous pyelogram revealed a slight irregularity of the calyceal pattern on the right. Retrograde pyelogram then demonstrated a mass at the upper pole of that kidney. Nephrectomy confirmed the impression of hypernephroma. The fever disappeared promptly following removal of the kidney and she was well 3 years later.

Fever as a sign of renal carcinoma is, of course, well known. Usually, however, the diagnosis of a fever-producing hypernephroma is not difficult since other signs are present. For example, in 273 patients with renal carcinomas reported by Berger and Sinkoff (32), 44 had fever but only 7 had pyrexia as the sole manifestation. It has been pointed out, however, that the diagnosis of renal carcinoma may be extraordinarily difficult particularly since some tumors produce little or no defect in the pelvis or calyces on pyelography. Lateral expansion of the tumor may result in only slight displacement of the kidney or increase in its size (33). This was the case with our patient, since she had at least 3 "negative" intravenous pyelograms during her long course. A clue which went unappreciated was a slightly high alkaline phosphatase. This enzyme has been found in increased quantities in several patients with hypernephroma and the level has returned to normal following nephrectomy (34). It is said that persistence of fever following removal of a hypernephroma is strong evidence of the existence of metastasis (35).

The second patient in this group had an anaplastic carcinoma of the lung, which was difficult to visualize radiographically. At a second bronchoscopic examination histologic evidence was obtained. Pneumonectomy resulted in lysis of fever, but involvement of hilar nodes implied a poor prognosis. The resected specimen contained an area of infection distal to the tumor mass, and it is likely that infection rather than tumor was responsible for the fever. In a series of 100 patients analyzed by Bloomer and Lindskog, fever was never the presenting symptom (36).

Lymphomas and Leukemias

Lymphosarcoma and reticulum cell sarcoma. Four patients with these diseases all had widespread involvement of abdominal and retroperitoneal nodes, and the disease was far-advanced when the diagnosis was finally made by biopsy. Lymphomas constitute the most common tumor of the retroperitoneal space; this area is notorious for its clinical silence and is an ideal site for the multiplication of cancer cells (37). The disease is usually widespread before displacement of the kidneys, stomach or colon becomes apparent radiographically. Deviation in the course of the ureter, as demonstrated by intravenous pyelogram, may be the earliest clue; this was true of two of our patients.

Hodgkin's disease. Two patients had courses

fairly typical of Hodgkin's disease. In one of them arthralgia delayed the diagnosis, while "collagen" diseases were being considered. Biopsy of a cervical node provided the correct answer. She is receiving intermittent therapy with triethylene melamine—the only survivor in this group. The other patient had had chills and fever for several months; chest x-ray revealed a slight widening of the mediastinum and the diagnosis was established by supraclavicular node biopsy. Both patients had Pel-Ebstein fever, which is said to be a disappearing phenomenon in Hodgkin's disease. A likely explanation for the reduction in the incidence of Pel-Ebstein fever is that present-day methods of treatment with steroid hormones, radiation therapy or radiomimetic agents may affect the temperature course in such a way that the classical periodicity does not become evident. In one of our patients administration of salicylates had little effect on the course of the temperature fluctuations, an experience which has been noted by others (38).

Monocytic leukemia. Two patients with monocytic leukemia gave great difficulty in diagnosis, and, in fact, the nature of their disease was determined only by autopsy. The first was a 41-year-old woman who had complained of fever, back pain, weakness and nervousness for 6 weeks prior to admission. The only noteworthy physical findings were thyroid enlargement and a few palpable nodes in the neck and axilla. There was severe anemia, the hematocrit ranging between 20 and 29 per cent. The white blood cell count was normal with a slight shift to the left and 8 per cent monocytes. Bone marrow was not diagnostic of any hematologic disorder. The appearance of a small infiltrate in the left upper lobe prompted a vigorous search for tubercle bacilli. Her condition deteriorated rapidly over the next 6 weeks; terminally, nucleated red cells appeared in the blood and the alkaline phosphatase rose to 23.8 Bodansky units. Autopsy revealed monocytic leukemia involving the bone marrow, liver, spleen, kidney, adrenals and pituitary; there was evidence of extramedullary hematopoiesis and a small residual focus of nontuberculous pneumonia.

The second patient suffered the abrupt onset of paraplegia. Laminectomy showed infarction of the spinal cord at T6–T8. During the next several months there was a high spiking fever, initially attributed to pyelonephritis or infection in a decubitus ulcer. However, the persistence and height of the fever despite treatment of these processes, led to consideration of other causes for fever. Biopsy of bone marrow, liver, skin and muscle and exploratory laparotomy, together with numerous bacteriologic, serologic, and radiographic examinations gave unhelpful results. Just before death a hemorrhagic rash appeared on the legs. This was thought to be due to an allergy to a drug. In addition there was noted terminally a palpable spleen and some enlargement of the liver. At autopsy, findings typical of monocytic leukemia were discovered in many organs.

Of all the leukemias, the monocytic type is notoriously difficult to recognize. We were interested to note that this was the only form of leukemia in the present series. The course in these patients tends to be subacute, lasting several months. Such manifestations as oral lesions, and presence of blast cells in the peripheral blood are often absent. Most cases described in the literature are characterized by a vague onset, weakness and symptoms of anemia. Fever may be a prominent symptom and 1 of the 8 cases described by Sinn and Dick was for some weeks a problem in diagnosis of unexplained fever (39). The clues to the diagnosis usually lie in some hematologic abnormality—either anemia, leukopenia or thrombocytopenia—which may antedate by months and even years the appearance of the full-blown picture of leukemia. Bone marrow examinations show a normal or aplastic picture, and immature cells in the marrow may not be found (40).

The diagnosis in the second patient was confused by the presence of several acute infections, which were held responsible for the fever. The significance of fever in acute leukemia has recently been studied by a group at the National Institutes of Health (41). Of 92 febrile episodes in their patients with acute leukemia, 59 were clearly related to infection. On the basis of these studies, the authors recommend that fever in patients with leukemia be considered due to infection until proved otherwise.

COLLAGEN DISEASES

Rheumatic Fever

Six of the 100 cases are now regarded as having suffered from acute rheumatic fever. This

diagnosis was always among those given prominent consideration, but in the absence of the full-blown picture satisfying Jones' criteria (42) the diagnosis cannot be made with certainty, and one must depend on the long-term course of the illness for a reasonably certain answer. It is inevitable, therefore, that some cases of rheumatic fever would appear in a series compiled in the manner of this one. The principal problems in our cases were to distinguish between acute rheumatic fever and such diseases as rheumatoid arthritis, systemic lupus erythematosus, bacterial endocarditis and tuberculosis.

The ages of these six patients were 15, 29, 36, 42, 59 and 70 years. Active rheumatic fever is not rare in middle-aged or elderly persons (43, 44), and may be encountered more commonly in the future, because of the availability of effective prophylaxis and therapy for streptococcal infections in young persons. Two of our patients had histories of previous rheumatic fever. In 3 the present illness had begun with soreness of the throat. Three had arthritis or arthralgia involving several joints. Repeated electrocardiographic examinations revealed "acute changes" in 3 of them. Heart murmurs were described in 4, but only one was a diastolic murmur. One of the 2 without any murmur had a transient pericardial friction rub. The oldest patient in the series had moderately severe congestive heart failure with cardiac enlargement during her illness. Leukocyte counts were normal in 3, elevated in 3, with one of the latter group having a count of 60,000 per cu. mm. on one occasion. The antistreptolysin titer was elevated in 4, normal in 2 patients. Fever and symptoms responded well to acetylsalicylic acid therapy in 4, and to ACTH in one case. Only one patient, the youngest, had a skin lesion, but in that instance the development of typical erythema marginatum was of considerable help in pointing to the correct diagnosis.

Rheumatic fever stands out in the present series of cases as the entity in which the findings on physical examination, and the course of the illness, were of paramount importance in diagnosis.

Systemic Lupus Erythematosus

During the 5-year period of this study it is estimated that between 20 and 25 new cases of systemic lupus erythematosus were recognized among our hospital patients. Thanks principally to the ready availability of the L.E. test, rapid diagnosis was possible in most of those. There were, however, 5 cases in which early diagnosis by the L.E. test could not be made, and since all had fever as a prominent manifestation they are included in this series of cases of prolonged febrile disease of obscure etiology. As was true of our cases of rheumatic fever, it can be said here that the diagnosis of lupus erythematosus was under serious consideration from the beginning in all of the cases, but immediate differentiation from such other diseases as hematogenous dissemination of tuberculosis, acute rheumatic fever, rheumatoid arthritis, acute glomerulonephritis, bacterial endocarditis, etc. could not be made with certainty. In 2 of these 5 cases the L.E. phenomenon eventually became demonstrable and they can be considered unequivocal cases. In the remaining 3, however, a positive test was never obtained; furthermore even after their deaths (2 by bacterial pneumonia, 1 by renal failure) typical morphologic evidence of this disease was not found. This may be due in part to the fact that all had received intensive steroid therapy, which may have made the histologic evidences of the disease less conspicuous. All 3 of these cases were characterized by typical skin lesions and other manifestations, such as arthritis, pleural effusions, active renal disease, etc. We feel justified in this diagnosis despite the absence of substantial proof. The data of Harvey and his associates are of interest on this point (45). They report negative L.E. tests in 19 of 96 cases with unequivocal systemic lupus erythematosus. Thirty-eight of their cases were examined at autopsy. Of those, 16 had severe complicating infection, but among the 22 without complicating infection were 5 cases in which little evidence of structural change could be found. One of their pathologists is quoted as remarking that the findings were "as if they had died a 'chemical death,' leaving behind no structural clues as to its nature."

Unclassified Collagen Disease

Two male adults, each about 25 years of age at the onset of his illness, have had rather similar chronic illness, characterized at times by high fever. The duration of illness in one patient is 13 years, in the other it is 3 years. These two diseases seem to belong in the general category

of collagen disease, since there are resemblances to systemic lupus erythematosus, rheumatoid arthritis and rheumatic fever. They are presented in a separate category, however, because it is thought they may represent a special syndrome.

In both men the illness began suddenly, with high fever and sore throat. The fever continued for weeks, and reached levels of 105 and 106°F. Cultures of throat and blood revealed nothing of significance. The hematologic response was distinctive, in that each had leukocytosis in the range of 20,000 to 35,000. Their illnesses have waxed and waned, but neither patient has been completely free of fever and other manifestations at any time since the onset. They have been subjected to the most searching study: roentgenograms, bacteriologic and serologic tests, skin tests, biopsies, etc. Antistreptolysin titer, sheep cell agglutination test (Rose), and L.E. test have been consistently negative in both patients.

Some months after the onset of illness both patients began to have rheumatic manifestations, with arthralgia, muscle pain and stiffness, and occasional true arthritis with joint swelling, and some atrophy of the adjacent muscle groups. For the most part the joints involved have been large ones. The rheumatic manifestations have come to be the patients' chief complaints and their appearance at the present time is more like rheumatoid arthritis than any other disease. Neither patient has shown evidence of renal, pulmonary or pleural involvement. Neither received much benefit from treatment with acetylsalicylic acid, but both showed great symptomatic improvement by steroid administration. However, this seemed to be merely a damping of the intensity of the process, since both patients continue to have low-grade fever, and suffer some discomfort because of muscle and joint pain.

PULMONARY EMBOLIZATION

Fever is a well known manifestation of pulmonary infarction, though its duration ordinarily is a matter of only a few days (46). In 3 of our cases, however, recurrent infarction of the lungs eventually was identified as the cause of long-continued fever. The disease predisposing to pulmonary embolization differed in each case. One was that of a 68-year-old woman who had been kept in bed for two weeks because of coronary insufficiency. A nightly temperature elevation to 102–103°F began, and persisted for the next 4 weeks. Examination in the hospital revealed basal pulmonary congestion and a small pleural effusion. Tests for tuberculosis, bacterial pneumonia and collagen-vascular disease gave negative results. During the fourth week in the hospital thromboembolic disease was suggested by the appearance of tenderness in the right thigh, and a transient pleural friction rub. Administration of heparin was begun, and within 4 days her fever subsided, and all other symptoms ceased. The use of anticoagulants has been advocated as a therapeutic trial in suspected cases of pulmonary infarction (47); we have observed several patients with overt pulmonary infarcts who became afebrile coincident with employment of anticoagulant treatment.

The second patient was a 41-year-old woman who had gradually developed signs of heart failure over a period of several years. The etiology of her heart disease was undetermined, although fluctuating antistreptolysin-O titers suggested the possibility of rheumatic myocarditis. However, she failed to improve after treatment with salicylates or adrenal cortical hormones. Terminally she developed signs of thrombophlebitis and pleuritic pain. Autopsy revealed dilatation and hypertrophy of the heart with foci of myocardial sclerosis. There were mural thrombi in the right ventricle, and multiple old and recent clots in the pulmonary vessels with areas of infarction distal to them. The course and findings are compatible with those of the disease called endocardial fibroelastosis of the adult type (48).

The pathogenesis of the fever in this patient is of interest. It is conceivable that fever was secondary to disease of the myocardium, but this seems unlikely in view of the fact that pathological changes in the myocardium were limited to fibrosis and no significant foci of inflammation were seen. Heart failure can in itself cause low-grade temperature elevations (49, 50). We believe, however, that the most likely cause for fever was recurrent infarctions of the lung. The multiplicity of lesions of different age is in keeping with the view that repeated emboli are a prerequisite for prolonged fever, and that a single embolus is probably associated with but a brief elevation in temperature.

The third patient, a 38-year-old man, had

an acute febrile illness lasting just 5 weeks and associated terminally with jaundice, cough, pleuritic pain and petechiae and ecchymoses. The laboratory data were consistent with a severe hemolytic anemia and thrombocytopenia. Terminally he had nitrogen retention and massive edema. Thromboembolic disease was obviously present and he was treated by anticoagulants and bilateral femoral vein ligation, but expired. Autopsy revealed numerous pulmonary emboli and infarcts. In addition there were thromboses of the inferior and superior vena cavae, and the renal and mesenteric veins. This case resembles the entity which has been termed visceral thrombophlebitis migrans (51), although hemolytic anemia has not been mentioned as part of this syndrome. Possibly hemolysis was responsible in part for this patient's fever.

HYPERSENSITIVITY STATES

Erythema multiforme. A 56-year-old white man complained of chills and fever for 2 weeks, and was found on examination to have tender muscles and papular lesions over his legs. Biopsies of the liver and skin showed mild acute inflammatory changes about small arteries, and he was first thought to have periarteritis nodosa. However, his symptoms and signs subsided spontaneously during 2 weeks in the hospital, and on follow-up examination 4 years later he appeared to be entirely well. While it is possible that he had periarteritis nodosa, the course of illness was not the usual one of that disease, and it seems more reasonable in retrospect to list him as an example of erythema multiforme. The etiology of that disorder is obscure but it is generally thought to be a "manifestation of hypersensitivity" since it frequently occurs following ingestion of drugs, particularly phenolphthalein derivatives, bromides, sulfonamides and salicylates, and tends to recur in some patients.

Drug fever. It is important to keep in mind the fact that fever is one of the most frequent systemic manifestations of hypersensitivity and that the drugs used to combat infection may themselves give rise to sensitization and pyrexia. A great many of them have been shown to be capable of causing fever, but penicillin, sulfonamide, propylthiouracil, iodides, and barbiturates are among the most common offenders (52). Apparently, however, almost any drug can do this occasionally, and there may be no other signs or symptoms of hypersensitivity. When fever is caused by one of the agents known to be a frequent offender, such as penicillin or a barbiturate, the diagnosis may not be difficult, but when fever is caused by a drug which has been given "routinely", for sedation or analgesia, the diagnosis may be more elusive. Such was the case in one of our patients who entered the hospital because of an acute pulmonary infection but continued to have fever for four weeks after resolution of the pulmonary infiltrate. At that time consideration was given to the fact that she was receiving phenylhydantoin (Dilantin) because of ill-defined seizures which had occurred some months previously. The therapy was discontinued, and her fever subsided promptly. Toxic potentialities of this drug, notably rash, leukopenia and hyperplasia of the gums, are well recognized; fever, however, is relatively rare although it has been reported as part of a generalized reaction characterized by jaundice and exfoliative dermatitis (53).

Granulomatous hepatitis. Liver biopsy may be the best practical means of identifying diseases characterized by the formation of granulomas, and occasionally it is possible to make an etiologic diagnosis by this means. In certain metazoan infestations recognizable fragments of larvae may be demonstrable, and now and then in such infections as histoplasmosis, tuberculosis or actinomycosis the parasite may be identifiable. More often the finding of granulomatous disease in the liver is a valuable adjunct to etiologic diagnosis, as was the case in patients with sarcoidosis and brucellosis in the present series. In 2 additional cases granulomas were found in liver tissue obtained by needle aspiration, but there was no other sound basis on which to establish an exact diagnosis. They are therefore listed simply as granulomatous hepatitis.

The first was a 32-year-old man who had been treated with a sulfonamide compound for acute pyelonephritis 3 weeks previously. One week before admission he complained of chilly sensations, fever and malaise. On entry to the hospital he was found to have fever of 104°F, and enlargement of liver and spleen. His temperature fluctuated between 101°F and 103°F for the next 3 weeks in the hospital, then subsided gradually without specific treatment. Ex-

tensive investigations were carried out but the only positive findings were in the demonstration of granulomas in the liver and bone marrow. This man then made a complete recovery, and was in good health at the time of follow-up 2 year later.

The second patient, a woman aged 71, who was known to be sensitive to penicillin, had been given a sulfonamide and tetracycline for an ear ache four weeks before admission. Shortly thereafter she began to have a remittent fever, and suffered some myalgia and chilly sensations. On admission to the hospital her temperature was found to vary between 101 and 103°F. There were no remarkable physical findings. Laboratory tests showed mild anemia and leukocyte count of 19,000, with 4 to 7% eosinophils. Numerous cultures for bacteria, fungi and acid-fast bacilli were negative, as were skin tests, agglutinations, extensive radiologic studies and bone marrow examinations. Liver function studies showed 34% bromsulfalein retention, and alkaline phosphatase was elevated to 29 Bodansky units. Liver biopsy revealed diffuse granulomatosis. Her fever subsided after 2 weeks in the hospital, and liver functions returned to normal. Two years later she was reported to be in good health.

In view of the failure to find evidence of specific diseases known to cause granulomatosis, and of the subsequent clinical recoveries of these 2 patients it seems reasonable to postulate that these illnesses were the result of hypersensitivity reactions. The second patient had other evidences to support the diagnosis of an allergic reaction—eosinophilia and a history of penicillin sensitivity. Both of our patients had been given sulfonamides, drugs notorious for producing a multiplicity of lesions, including granulomas. In 22 patients who were thought to have "sulfonamide" lesions at autopsy, granulomas were found in the liver in 8; 2 of these patients had also been febrile (54). It is of interest also that granulomas can be produced in dogs by the administration of sodium sulfadiazine, although the lesions are usually limited to the kidneys and myocardium (55).

NON-SPECIFIC PERICARDITIS

In retrospect, and on the basis of adequate follow-up observation, this diagnosis appears probable in the cases of 2 elderly men, aged 68 and 71. In both of them fever was the predominant clinical manifestation, ranging between 101 and 104°F. One patient had recurrent attacks of pain in the left lateral chest in association with daily remittent fever for 18 weeks. A transient pericardial rub was occasionally audible, and the electrocardiogram showed changes compatible with pericarditis. Initially the diagnosis of acute "benign" pericarditis was favored but this was questioned later because of the long duration of illness. Diagnostic tests for other causes of pericarditis were all negative. His symptoms were eventually controlled by a long course of steroid therapy, and did not recur when this was terminated. Two and one-half years later he was asymptomatic and appeared well.

The second patient's febrile illness lasted 9 weeks, and the clinical problem was similar, except that chest X-ray revealed bilateral pleural effusion in addition to the pericardial effusion. These roentgenographic signs cleared without specific therapy during a period of 3 weeks.

Because of the ages of these 2 patients the so-called post-myocardial-infarction syndrome (56) had to be given consideration. However, there was no evidence of recent myocardial infarction in either case, and the duration of their febrile periods is longer than has been described.

Non-specific or idiopathic pericarditis is at best a diagnosis which must be made by exclusion. Evidence tending to implicate the Coxsackie viruses or infectious mononucleosis is occasionally obtained, but in most instances no specific etiology can be established. Fever may be a prominent feature of this syndrome. In Levy's series, 20 of 27 patients had fever, ranging between 100.4 and 105°F and lasting as long as two months; indeed, prolonged fever of obscure origin was the chief problem in one of his cases (57). It is noteworthy that pericardial rub may be absent in a significant number of cases, and that pulmonary infiltrations or pleural effusions are not uncommon (58).

SARCOIDOSIS

Fever is usually believed to be so rare an accompaniment of sarcoidosis, that its presence should suggest a search for some complicating disease (59, 60). Nevertheless 2 of the patients in our series had fever as a prominent manifestation.

The relation between erythema nodosum and

sarcoidosis is of special interest here since erythema nodosum is characterized by fever. This entity has been thought to be a manifestation of a number of infections, particularly those caused by the tubercle bacillus and the hemolytic streptococcus. Lofgren, however, has presented evidence that erythema nodosum in the presence of hilar lymphadenopathy, fever and arthralgia represents the first, or "lymph node", stage of sarcoidosis (61).

One of our cases seems to provide a typical example of the hilar-lymph-node syndrome. She complained of fever and night sweats for 3 weeks, and was found to have enlargement of the liver and spleen. While in the hospital the characteristics of erythema nodosum made their appearance, and chest x-ray revealed enlarged hilar glands bilaterally. The tuberculin test was weakly-positive in 1:100 dilution, and the serum globulin was 4.7 Gm per cent. Biopsy of axillary and supraclavicular nodes and of the liver revealed granulomata and no acid-fast bacilli. Fever subsided without specific therapy, although it is of interest that aspirin aggravated her malaise and myalgia. The patient still had hilar adenopathy 3 months later although she was entirely well. As judged by Lofgren's observations the prognosis is good, since only 8 per cent of patients progressed to the stage of chronic pulmonary disease (62).

The second of our patients, a 62-year-old white man had fever as high as 103°F and shaking chills for 4 weeks. One week before admission he developed severe conjunctivitis and tender spots under the fingernails. Physical examination revealed an acutely ill man with splinter hemorrhages of the nail beds and petechiae. He had a severe conjunctivitis but the iris was spared. There was no heart murmur or enlargement of liver and spleen. The initial diagnosis was bacterial endocarditis, but 20 negative blood cultures, failure to develop a heart murmur and unsuccessful trials with numerous antibiotics argued against this diagnosis. The diagnosis of sarcoidosis was suggested by a left hilar mass, weakly positive tuberculin test, peculiar papular rash and hyperglobulinemia. Liver biopsy was normal but a lymph node removed from the hilar area of the left lung revealed granulomata of sarcoidosis. His fever gradually subsided over a period of 3 months, and chest x-rays 6 months later showed a reticular infiltrate compatible with the diagnosis of sarcoidosis. Five years later the infiltrate had not changed. Despite the confusing picture at the onset of the illness, it seems probable that this patient had sarcoidosis, although we cannot exclude the possibility that this syndrome developed in response to a specific infectious disease, e.g. hemolytic streptococcal infection. Regarding the splinter hemorrhages it is interesting to note that a careful study indicates they are in no sense pathognomonic of endocarditis (63).

CRANIAL ARTERITIS

Two elderly women, ages 67 and 73, had febrile illnesses which were eventually regarded as being due to giant cell (cranial) arteritis. In one the diagnosis was substantiated by biopsy of the temporal artery. Her illness had begun 12 weeks previously, with fever, malaise and chills, which seemed to follow an injection of typhoid vaccine. She had been admitted to another hospital and had received antibiotic treatment without effect. The principal laboratory finding was moderate leukocytosis with 8 to 12 per cent eosinophils. She complained of severe headache at times. After some days in our hospital she had a recurrence of the severe headache, and that symptom led to a careful palpation of the temporal arteries; one of them was found to be thickened, though it was not tender. Biopsy revealed the typical histologic picture. Steroid therapy was begun and brought about prompt subsidence of fever and relief of headache. When the treatment was terminated after two months, there was no recurrence of symptoms, and follow-up inquiry 2 years later revealed that the patient felt quite well.

The second patient was admitted to the hospital twice during a 4-month period, because of fever in the range of 101–102°F. Her symptoms had begun following a tooth extraction. In addition to the fever she complained of mild joint pains. Because of that the tentative clinical diagnosis for a time was rheumatoid arthritis. She also had some headache, as well as vague pains in the mastoid and parotid regions. Her leukocyte count was 9,000–11,000, with 2–4% eosinophils. Three months after the onset of fever she experienced sudden impairment of vision; visual field studies revealed bilateral right inferior quadrantic defects. This raised the possibility of cranial arteritis, although palpable abnormality of the temporal and occipital vessels could not be found, so a biopsy was not

done. Her fever and other symptoms gradually subsided at the end of 6 months, and did not recur. The diagnosis in this case is based on clinical findings, course of illness, age of the patient, and especially on the sudden occurrence of visual defect in the distribution of the cerebral optic radiations.

This disease deserves special consideration in elderly patients with unexplained fever. Severe headache is an uncommon complaint in persons of this age period, and, when combined with fever, is probably a sign of serious disease. In view of the present evidence that prompt treatment with adrenal steroid hormones may reduce the incidence of visual impairment (64) early recognition becomes particularly desirable.

PERIODIC DISEASE

In 1947 and 1951 Reimann pointed out the possible interrelationship of a group of periodic disorders, characterized by such manifestations as fever, abdominalgia, arthralgia, neutropenia, purpura and edema (65, 66). He suggested that they be grouped under the term Periodic Disease, and described them thus: "of unknown origin, often begin in infancy, recur uniformly at predictable times for decades without affecting the general health and resist treatment." The regularity of the recurrences was stressed, and emphasis was placed on the point that the cycles were frequently 7 days in length, or in multiples of seven, as 14, 21, 28 and 56 days. He mentioned that "seven always has had a special significance and looms large in folklore," and, in discussing possible etiology, remarked that "some cosmic association may be suspected."

It seems to us that Reimann performed a valuable service in directing the attention of American clinicians to this kind of periodically recurring disorder, and that his designation for it is satisfactory for the present. However, there seems to have been a peculiar reluctance to accept the concept, and this group of disorders receives little or no mention in our textbooks of medicine. A possible reason for this skepticism may be the emphasis placed on associations with the figure seven and cosmic influence. Actually, some of the cases quoted by Reimann had illnesses recurring at irregular intervals and the cycles were from 2 days to 6 months or even longer.

The cases in our series seem to resemble closely some of those described by Reimann. Our 5 patients were all males, ages 33, 33, 42, 53 and 54 years. Their episodes of febrile illness had been occurring for 10, 25, 23, 7 and 25 years. Two of them stated that parents or siblings were subject to similar episodes. The intervals between attacks were 7–9 days in one, 3–4 weeks in another, and 2 or 3 times a year in the other three. All were in good general health between episodes and able to hold responsible positions; however, all found it necessary to go to bed during attacks. The duration of the episodes varied from 1–2 days to several weeks. The chief complaints were sudden onset of malaise and fever, with temperatures reaching 101° to 105°F. Joint pains and skin manifestations were denied, but 3 of them stated that abdominal pain was sometimes present. Three had moderate leukocytosis during their attacks and splenomegaly was noted in 3. Otherwise, extensive studies in our hospital, as well as in other clinics, had not yielded findings of significance.

One of our patients is of special interest because he manifested some abnormalities which may have provided a clue to the pathogenesis of his disorder. The patient was a physician, aged 33, who had had bouts of fever since the age of 8. During investigation of his illness at another hospital it was noted that he gave a history of salt-craving and hyperpigmentation, and this had led to studies of his adrenal cortical function. These revealed a fall in eosinophils but no rise in 17-ketosteroids following an infusion of ACTH. He was also found to have increased excretion of pregnanetriol in the urine. The possible existence of a mild form of adrenogenital syndrome had therefore been suggested. During the course of his study in our hospital, Dr. Philip Bondy was consulted regarding the disordered adrenal function. Dr. Bondy then suggested that the entire clinical picture could conceivably be due to an abnormal metabolism of steroid hormones, citing the finding of Kappas et al. (67) that etiocholanolone is capable of inducing fever and malaise in man. Subsequent tests of our patient did in fact reveal the presence of abnormal quantities of unconjugated etiocholanolone in the blood during febrile periods, whereas this steroid was absent when he was free of symptoms. Dr. Bondy and his associates carried out similar observations on one of the other 4 patients with periodic disease, and he too showed this abnormality of

steroid metabolism (68). Much more work will be needed to assess the significance of these findings, particularly on the question of whether unconjugated etiocholanolone may be found in the blood during other kinds of febrile disease.

Another entity, which closely resembles periodic disease, and, doubtless has been confused with it, has recently been characterized by Heller et al (69), who have suggested the name Familial Mediterranean Fever. They describe 74 cases personally observed in Israel, together with 179 cases culled from previous reports in the medical literature, some of which had been labelled periodic disease. Familial Mediterranean Fever has so far been recognized almost exclusively among Jews and Armenians, and there is a tendency for more than one case to occur in a family. Symptoms usually begin before the age of 10 years, and consist of bouts of fever with pain in abdomen, chest or joints, and, in some cases, erysipelas-like lesions on the extremities. Some patients show evidence of renal dysfunction, probably because of amyloidosis.

It is possible that one or more of the cases we have labelled periodic disease is actually an example of Familial Mediterranean Fever. Our records do not contain adequate information regarding ethnic background to assist in classifying them in retrospect. At any rate, the lead about possible role of etiocholanolone in periodic diseases and the genetic aspects of Familial Mediterranean Fever tend to implicate metabolic disorders in the etiology of both kinds of febrile disease.

Recently Priest and Nixon (70) have reviewed reports on these periodic illnesses, and suggested that a new name be applied to them: familial recurring polyserositis. It is obvious that the confusion will not be resolved until we have clearer concepts regarding pathogenesis.

MISCELLANEOUS DISEASES

Weber-Christian disease. The patient was a 66-year-old physician who had fever for 3 weeks before entry. At the onset of his illness he had had fairly typical erythema nodosum. When seen in our hospital he showed edema of the legs and feet, and enlargement of the spleen. As the edema receded, subcutaneous nodules were found to be present on the extensor surfaces of the legs. Biopsy of one of these revealed panniculitis and arteritis compatible with the histologic picture of Weber-Christian disease. There was considerable improvement in the fever and cutaneous lesions when ACTH was given. In contrast to other cases in this series in which there were atypical symptoms of relatively common diseases, this patient suffered from a relatively straightforward, but rare entity. Fever, tender nodules on the extremities, erythema nodosum and anemia have all been found in other cases of Weber-Christian disease (71). Our failure to consider that possibility accounted for the delay in diagnosis.

Thyroiditis. A 53-year-old woman noted afternoon temperature elevation to 103°F 8 weeks before admission. Two weeks after onset of fever she began to have pain in the jaw and neck. Several teeth were extracted, but without improvement, and the patient was admitted to the hospital for further study. Physical examination revealed slight enlargement of the thyroid, which was barely tender. The temperature ranged between 100 and 102.4 in the hospital. The diagnosis was established by the laboratory findings typical of thyroiditis—I^{131} uptake of 7.5 per cent, butyl extractable iodine of 7.8 mcg. per cent and serum precipitable iodine of 11.0 mcg. per cent. Tests for other causes for fever were unproductive. There was a salutory response to prednisone therapy.

Fever is commonly present in the syndrome of subacute thyroiditis, and its duration may be long. In a series of cases from the Presbyterian Hospital, New York (72), fever was present for 3–8 weeks. Thirty-three of 38 patients reported by Crile had fever, which was present for weeks and even months (73). Usually, of course, swelling and tenderness of the thyroid gland makes the diagnosis simple but the peculiar radiation of the pain to the back of the neck, jaw and throat has in some instances led to the incorrect diagnosis of meningitis, impacted wisdom teeth and tonsillitis. It is of interest that several of Crile's patients underwent dental extractions, as did our patient.

The most definitive method of making the diagnosis of thyroiditis is, of course, biopsy. Studies of thyroid function, which characteristically demonstrate depression of I^{131} uptake and usually elevation of blood iodine levels, and demonstration of antibodies against thyroglobulin, may be helpful.

Rupture of the spleen and pancreatitis. A 35-year-old man had a brief episode of fever, chills and malaise 3 months before admission. Two months later he developed fever, rigors, malaise and upper abdominal pain. On admission to the hospital physical examination showed only the signs of a small left pleural effusion. He was anemic and the leukocyte count was 16,900. Blood sugar, serum amylase and electrolytes, liver function tests, sputum studies for tubercle bacilli, bronchoscopy and bronchography were normal.

Although the source of his difficulty was first thought to be in the thorax, a retroperitoneal mass was later demonstrated by radiologic studies. Exploratory laparotomy disclosed the presence of a ruptured spleen with intracapsular hematomata and necrotizing pancreatitis involving the tail of the pancreas. Removal of the spleen and parts of the pancreas resulted in complete recovery.

It is interesting to speculate upon the course of events in this case. Rupture of the spleen may have occurred spontaneously at the time of fever and malaise 3 months before. Although spontaneous rupture usually involves diseased spleens notably in patients with leukemia, malaria or infectious mononucleosis, it may also be seen in previously healthy organs following minor trauma. The usual symptoms of splenic rupture are left upper quadrant pain and collapse, but fever may be the dominant sign (74). Perhaps our patient had infectious mononucleosis at the onset of his illness.

Pancreatitis has not, to our knowledge, been reported following rupture of the spleen, but certainly occurs after splenectomy, particularly when there is difficulty in dissecting the spleen from the tail of the pancreas.

Pancreatitis may have antedated splenic hemorrhage here, presumably due to erosion of a vessel by liberation of pancreatic enzymes. Such a course of events has been reported (75). It seems worth while to emphasize that pleural effusion is frequently a clue to disease below the diaphragm as well as above it, and is a common finding in acute pancreatitis (76). Consideration of this association might have led to earlier correct diagnosis in our patient.

Myelofibrosis. A 62-year-old man had fever, chills, drenching sweats and myalgia for 9 months. Treatment with various antimicrobial drugs had been without effect. On examination he was found to have ulcerations and petechiae of the oral mucosa and enlargement of the liver and spleen. Pertinent laboratory data were hemoglobin of 8.1 Gm. per cent, leukocyte count of 16,100, with a shift to the left, and 13 nucleated red blood cells per 100 leukocytes on the peripheral smear. Reticulocyte count was 4.2 per cent and platelet count 60,000. Liver biopsy showed extramedullary hematopoiesis. Two bone marrow aspirations were unsuccessful but a bone marrow biopsy revealed fibrosis. Extensive search for evidence of other febrile diseases, especially tuberculosis, gave negative results. The temperature, which had reached 105°F. nightly, fell to normal following administration of aspirin, and remained within the normal range while he received 10 mg. prednisone per day.

Fever must be a rare occurrence in myelofibrosis and is not mentioned as a sign in 2 recent reviews (77, 78). Its presence in a patient with myelofibrosis should strongly suggest the diagnosis of tuberculosis in addition to the hematologic disorder. One review which compares myelofibrosis with and without tuberculosis states categorically that pyrexia is the single most important sign which distinguishes myelofibrosis with tuberculosis from idiopathic fibrosis of the marrow (79).

There are a number of reasons for thinking that our patient did not have tuberculosis in addition to myelofibrosis. The course was too protracted; the clinical status of patients with tuberculosis and myelofibrosis has generally deteriorated rapidly. The tuberculin test was negative, and culture of the bone marrow did not yield acid-fast bacilli. His fever did not subside when streptomycin was given, and no granulomata were found when the spleen was removed 6 months after admission. He expired a year later at another hospital.

FACTITIOUS FEVER

Determination of the body temperature is so firmly incorporated in all clinical practice that the reliability of results is seldom questioned. Yet it is possible for patients to feign illness by falsifying their temperatures. Such was the case in 3 of the patients in this series, who masqueraded as diagnostic problems for long periods of time. Their case records, along with those of

11 others, have been reported in detail elsewhere (80).

The first patient, a 23-year-old woman, complained of fever and abdominal pain for several weeks following uterine curettage for spontaneous incomplete abortion. She was treated with penicillin, streptomycin, chloramphenicol, erythromycin and sulfonamides, but continued to be "febrile." Finally exploratory laparotomy was undertaken, but no abnormality could be found. Following operation the fever disappeared, and the patient later boasted to her room-mate that she had been deliberately shaking the thermometer in the wrong direction. As is true of most patients with factitious fever she had other evidences of abnormal behavior. The difficulty in recognizing the problem here lay in the fact that there was a plausible cause for illness.

The second patient was an 18-year-old student nurse who was seen in consultation at another hospital, because of intermittent fever of several weeks' duration. Inspection of the temperature chart revealed a discrepancy between the temperature fluctuations and the graphic record of her pulse; furthermore her general appearance was surprisingly good when considered in relation to a prolonged febrile illness. When confronted with the possibility that she might be falsifying the temperature readings, her "fever" terminated abruptly. The motives for this behavior and the exact means by which it was accomplished were not established. This patient provides an example of several common findings in factitious fever. She was a student nurse; in our experience nurses and others familiar with hospital routine are likely to be successful in this form of deception. She did not have tachycardia despite abrupt spikes in temperature. Other clues of this nature are failure of the temperature to follow the normal diurnal gradient, rapid defervescence unaccompanied by diaphoresis, and fever of 106°F or higher, a rare phenomenon in adults (81).

The most spectacular case of factitious fever was presented by a 38-year-old man, weighing 325 pounds, who complained of "black-out" spells. The history was bizarre and characterized by episodes of unconsciousness during one of which he was "pronounced dead." In addition, he had peripheral vascular disease which had required lumbar sympathectomy and a left mid-thigh amputation. Despite this there was no evidence of vascular disease elsewhere, and except for the amputation and sharply demarcated left hemi-anesthesia the findings on physical examination were normal. Numerous laboratory studies failed to reveal significant abnormality. In the hospital he had several sharp rises in temperature. Malingering was suspected when the temperature dropped from 106.6°F to 99.6°F in less than 4 hours without concomitant sweating or change in heart rate. Thereafter, with a nurse in constant attendance during temperature determinations his fever disappeared. He left the hospital against medical advice, but subsequent letters from other hospitals confirmed the diagnosis of factitious fever. Aside from the dissociation between pulse and temperature, this patient's fever was only one aspect of a factitious symptom complex.

Factitious fever must be differentiated from habitual hyperthermia—sometimes called psychogenic or hysterical fever (3). This disorder is most likely to occur in young women with overt neurotic traits in whom body temperature elevations to the neighborhood of 100°F occur frequently, even daily, for months or years. Habitual hyperthermia is probably a manifestation of vasomotor instability, much like labile hypertension or dermographia.

The diagnosis of fraudulent fever is not difficult if the possibility is considered. Attendance of a nurse at the time the temperature is recorded may solve the riddle. In some instances simultaneous oral and rectal temperatures will disclose a disparity. Finally, a thorough search of the patient's belongings for a cache of pre-set thermometers or a supply of vaccines, toxins, and syringes and needles may provide the answer. The prolonged courses of these "fevers" with intensive diagnostic study in many institutions, however, is proof that many of the patients avoid apprehension for long periods of time.

PATIENTS IN WHOM NO DEFINITIVE DIAGNOSIS COULD BE ESTABLISHED

Despite vigorous efforts, no diagnosis was established in 7 patients. Six of these, in all of whom the duration of illness was less than 2 months, made apparently complete recoveries. None developed significant anemia, weight loss or cachexia. In short, these illnesses resembled acute self-limited infections rather than prolonged, chronic disease.

The first patient, a 52-year-old woman, was

thought at first to have multiple myeloma and an infection. Confusing features in her case were moderate hyperglobulinemia and an elevation in the titer of cold agglutinins. Usually cold agglutinins are elevated only in primary atyical pneumonia but high titers have also been noted in mumps, hemolytic anemia, various liver diseases and some peripheral vascular disorders. In retrospect, the course of this illness is most compatible with a low-grade infection which subsided spontaneously.

The second patient presented a confusing problem characterized primarily by fever. Unexplained were leukocytosis, a slight rise in the titer of brucella agglutinins and the finding of "mild colitis" by x-ray. Fever receded following a course of tetracycline and streptomycin and 2 years later the patient felt well. Although the therapeutic response favors the diagnosis of brucellosis, the rise in agglutinin titer was not in the significant range. Furthermore, one might have expected spontaneous defervescence in less than 7 weeks in brucellosis. Salmonella enteritis has to be considered because of the radiologic findings and therapeutic response. However, leukocytosis is unusual in salmonellosis in the absence of metastatic abscesses. Another possibility is amebiasis, which can cause prolonged fever of obscure origin (82).

An even more convincing case can be made for amebiasis in the next patient whose illness was preceded by diarrhea and who had a persistent low-grade eosinophilia. More intensive examination of the feces for parasites might have led to the diagnosis. Therapeutic trial with antiamebic drugs is less popular now than formerly, but doubtless is justifiable in instances such as these.

Disseminated lupus erythematosus was the tentative diagnoisis at the time of admission of the 4th patient. The laboratory findings and subsequent course did not substantiate this and instead seemed to point more toward the category of "atypical infectious mononucleosis." The clinical findings were compatible, but the characteristic hematologic abnormalities and rise in heterophile agglutinin titer were lacking. Seronegative "infectious mononucleosis" has been described in a number of reports, and, in general, is said to be milder, associated with less pyrexia, a higher incidence of cutaneous eruptions and fewer abnormal lymphocytes, than the classical heterophile-positive form of the disease (83). Toxoplasmosis is also capable of producing this clinical picture in adults (84). Tests for this disease were not carried out in our patient.

The illness of the fifth patient was characterized by seven weeks of fever and recurrent bouts of abdominal pain. In retrospect, this may have been an infection by one of the Coxsackie viruses. While Bornholm disease, or epidemic pleurodynia is perhaps the prototype of infection with this virus, atypical forms presenting mainly with abdominal pain and fever have been described.

In the sixth patient in this group we probably have an example of two well known diseases occurring in sequence and causing relatively prolonged fever. The patient was first seen because of cough and chest pain and showed electrocardiographic evidence of an acute myocardial infarction. He subsequently developed hematuria, proteinuria, and excreted red blood cell casts. The clinical manifestations improved upon administration of steroid hormones. For a time he was thought to be suffering from periarteritis nodosa, but that diagnosis could not be substantiated by histologic methods, and he made an apparently complete recovery. We now feel that the best explanation for this course of events is that the patient had a myocardial infarction associated with considerable pericarditis, and that this was followed by infarction of the kidneys giving rise to transient hematuria and azotemia.

The last patient may have had thrombotic thrombocytopenic purpura. This syndrome (85, 86) consists of the triad of bizarre central nervous system manifestations, hemolytic anemia, and thrombocytopenia with hemorrhagic manifestations. Our patient had been under treatment for tuberculosis for several years when these symptoms made their appearance. In an effort to control his bleeding tendency splenectomy was performed but he succumbed shortly afterward, and permission for autopsy could not be obtained.

DIAGNOSIS IN FEVER OF UNKNOWN ORIGIN

The means by which the diagnosis was finally achieved in 93 patients is summarized in Table III. In several instances two procedures carried out at about the same time provided helpful information; for that reason the total in the table is 106. As mentioned in the previous sec-

TABLE III

Method of Diagnosis in 93 Cases of Fever of Obscure Etiology

Diagnosis	Number of cases	Biopsy	Laparotomy	Bacteriology	Serology	Other	X-ray	Clinical course	Response to Treatment	Autopsy
Infections										
Tuberculosis	11	4	1	4					4	1
Pyogenic	15		8	4			2		1	3
Bacterial endocarditis	5			3				1		1
Other	5	1		1	4	1				
Neoplastic diseases										
Disseminated carcinoma	7	6	1				1			
Localized carcinoma	2		2				1			
Lymphoma	8	5	1							2
No histologic diagnosis	2						1			
Collagen										
Rheumatic fever	6							6	2	
Lupus erythematosus	5				2			3		
Unclassified	2							2		
Cranial arteritis	2	1						1		
Factitious fever	3							3		
Periodic disease	5							5		
Pulmonary emboli	3							1	1	2
Non-specific pericarditis	2							2		
Sarcoidosis	2	1	1							
Hypersensitivity	4	3							1	
Miscellaneous	4	2	1			1		1		
Total	93	23	15	12	6	2	5	25	9	9

tion, no diagnosis could be made in 7 cases, and they will not be considered further here.

The cause of fever was not apparent until autopsy in 9 instances—this included 2 cases of monocytic leukemia, 1 miliary tuberculosis, 1 liver abscess, 1 subphrenic abscess, 1 ascending cholangitis, 1 abacteremic bacterial endocarditis and 2 with multiple pulmonary emboli. The fact that some of these were potentially curable diseases will be discussed in the section on Prognosis.

Histologic examination of tissue and exploratory surgery stand out as diagnostic procedures of special value in this kind of clinical problem, since in 23 instances the diagnosis was made by needle or excisional biopsy, and in 16 cases laparotomy or thoracotomy provided the needed information. When the atypical nature of most of the cases in this series is taken into consideration, the high yield of positive information by examination of tissue seems impressive. As might be predicted most of the disorders identified by biopsy were neoplastic disease or tuberculosis. Other diagnoses made by biopsy were cranial arteritis, sarcoid, granulomatous hepatitis, Weber-Christian disease and myelofibrosis.

It seems worth while to give detailed consideration here to biopsy as a diagnostic technique in this type of clinical problem. As is summarized in Table IV, one or more biopsies were performed in 58 of our patients, and in 23 of them this was the means of diagnosis. However in only 15 was the first attempt productive. Furthermore, there were 8 cases in which one or more excisional or needle biopsies were negative, yet a diagnosis could be made from tissue obtained at laparotomy. Exploratory laparotomy failed to provide the diagnosis in 2 patients, who were later found to have monocytic leukemia and systemic lupus erythematosus.

Of 95 biopsy specimens examined, 65, from 35 patients, were not helpful. Many of the uninformative biopsies were from patients with

TABLE IV

Value of Biopsy in Different Disease Categories

	Neoplastic diseases				Infections				Collagen diseases			Miscellaneous diseases								No diag. made	Total
	Disseminated carcinoma	Localized carcinoma	Lymphomas and leukemias	Presumed	Tuberculosis	Pyogenic	Bacterial endocarditis	Other	Rheumatic fever	Lupus erythematosus	Unclassified	Cranial arteritis	Factitious fever	Periodic disease	Pulmonary emboli	Non-specific pericarditis	Sarcoidosis	Hypersensitivity	Other		
Number of cases	7	2	8	2	11	15	5	5	6	5	2	2	3	5	3	2	2	4	4	7	100
Cases in which biopsy used	7	2	7	1	7	7	1	2	0	4	2	1	0	2	2	2	2	3	2	4	58
Biopsy diagnostic	6	0	5	0	4	0	0	1	0	0	0	1	0	0	0	0	1	3	2	0	23
Biopsy not diagnostic	1	2	2	1	3	7	1	1	0	4	2	0	0	2	2	2	1	0	0	4	35
Initial biopsy not diagnostic; subsequent biopsies diagnostic	3	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	8
Biopsy not diagnostic; laparotomy diagnostic	1	2	0	0	1	3	0	0	0	0	0	0	0	0	0	0	1	0	0	0	8

bacterial infections. In the case of liver tissue these showed only ascending cholangitis or nonspecific inflammatory changes. Other diseases in which biopsy was not helpful included the collagen groups, nonspecific pericarditis, and periodic disease. Almost one half of our biopsies were from the liver. This procedure is employed comparatively frequently in our hospital, not only when primary liver disease is believed present, but also because we regard liver tissue as likely to reveal the presence of generalized processes such as tuberculosis, sarcoid or lymphoma. Disease was detected by this method in patients without hepatomegaly and with normal liver function tests.

Biopsy of skin or muscle was helpful twice, but in both instances the patients had palpable and visible lesions. With regard to lymph node biopsy, our experience is in line with the general impression that any palpable node in the neck or axilla may provide diagnostic information, especially when tuberculosis or neoplastic disease are under consideration. We usually resist the temptation to carry out biopsy of palpable inguinal nodes, because they are so likely to show only 'nonspecific inflammatory change.' Bone marrow aspiration was of little help in this series of cases, but trephine biopsy did provide the diagnosis in 2 of the 4 cases in which it was done; in both of those x-ray had already disclosed the presence of some kind of bone disease. Renal biopsy was carried out twice and did not yield the correct answer in either instance.

Bacteriologic studies provided the diagnosis in 12 cases in the series. In 4 of them *M. tuberculosis* was demonstrated, and in 7 others the causative organism was eventually demonstrated in blood culture. Lastly, Gram-stain of synovial fluid revealed Neisseria in 1 case. Serologic tests were helpful in the diagnosis of brucellosis, psittacosis and gonorrhea.

Although x-rays were credited with being responsible for arriving at the correct diagnosis in only 5 cases, they provided valuable hints in a number of others. In patients with unexplained fever, radiographic study of the chest and intravenous pyelography should be among the first procedures to be done. Studies of the gastrointestinal and biliary tract are then indicated, and later a bone survey must receive consideration. Although none of these procedures stands out as being of particular value in the present series of cases it must be kept in mind that radiologic diagnostic tests were successful in hundreds of instances during the time period of this study. The cases under consider-

ation qualify for inclusion only because conventional diagnostic tests were not helpful.

The diagnosis of a number of diseases, particularly acute rheumatic fever, which may present in bizarre fashion in adults, and other collagen diseases, can only be made on clinical grounds, sometimes only after prolonged observation. The same applies to the diagnosis of recurrent pulmonary emboli, nonspecific pericarditis, and periodic disease. Recognition of factitious fever requires only that the clinician keep this possibility in mind.

Therapeutic trials are warranted under certain conditions, and may occasionally be of great value. In our group these included the use of isonicotinic acid hydrazine in tuberculosis, aspirin in rheumatic fever, heparin in thromboembolic disease and the withdrawal of drugs suspected of causing drug fever. Occasionally prompt response to bacterial infections such as brucellosis, tularemia or even pyelonephritis due to Gram-negative pathogens may be the principal means of diagnosis; usually, however, it is only confirmatory.

PROGNOSIS IN FEVER OF UNKNOWN ORIGIN

Of the 100 patients in the series, 32 succumbed to the disease responsible for fever. This included 17 of 19 patients with tumors, 5 with infections, 5 with collagen disease, 2 with pulmonary emboli, and 1 each with Weber-Christian disease, myelofibrosis, and suspected thrombotic thrombocytopenic purpura. Twenty of our patients, including 6 in whom no diagnosis could be established, recovered without specific therapy. In 10 there has been progress of disease or failure to improve; half of these are the patients with periodic disease, the remainder had collagen disease, Hodgkin's disease and sarcoid. Attention should be focused on the largest group, comprising 38 patients, who were eventually helped by specific medical and surgical therapy. Twenty-nine of these had infections, and 20, including 8 with tuberculosis, recovered following the use of proper chemotherapeutic agents. Nine patients required surgery in addition to antimicrobial therapy; all had abscesses in the abdominal cavity, pelvis, kidneys, gallbladder or liver. Aspirin and adrenocorticoids were of value in the collagen diseases, and steroids also induced remissions in cranial arteritis and nonspecific pericarditis. Therapy with anticoagulants resulted in disappearance of fever in one patient. The efficacy of specific therapy in these patients convinces us that the clinician should feel obliged to make unremitting effort to establish an etiologic dagnosis in a patient with prolonged unexplained fever.

Of special, indeed tragic, significance is the fact that 7 of the 9 patients in whom the correct diagnosis was made only at autopsy had diseases for which there is effective treatment.

CONCLUDING REMARKS

The Changing Spectrum of F.U.O.

It seems worth while to compare briefly this analysis with some others in the medical literature. Since 1930 several groups of patients with fever of unknown origin have been described, notably those of Alt and Baker (87), Kintner and Rowntree (88), Hamman and Wainwright (2), Keefer (89), Bottiger (90) and Geraci et al. (91). Comparison of reports such as these is difficult because the criteria employed for selection of patients have differed considerably. For example, more than half of Alt and Baker's 101 patients were febrile for less than three weeks, which would disqualify them from our study. In 90 of Bottiger's 158 cases the diagnosis had been made, or the symptoms had subsided within 10 days. It is reasonable to assume that the majority of his patients had self-limited viral infections. Inclusion of patients with prolonged low-grade fever, between 99° and 101°F, in some series skews the distribution toward habitual hyperthermia and nearly 50 per cent of those in Kintner and Rowntree's series fitted into this diagnostic category. The present report is the only one which was planned in advance as a prospective study. The others depended to some extent on review of charts in which the diagnosis at the time of discharge from hospital was unexplained fever.

Despite these obvious limitations certain trends, summarized in Table V, are apparent. There has been a lessening of pyogenic infection, particularly the varieties caused by Gram-positive cocci. On the other hand, infections with Gram-negative enteric pathogens appear to be increasing, perhaps as a consequence of antibiotic therapy (92). The continued importance of tuberculosis as a cause of prolonged pyrexia is noteworthy and bears out the contention that

the prevalence of this disease has not changed greatly, despite lowering of the morbidity and mortality (93). The relatively low incidence of tuberculosis in the series of Geraci *et al.* may be due to the fact that their material was limited to cases of tuberculous peritonitis discovered at laparotomy, while all other studies included tuberculosis of lung, lymph nodes and liver. Cases of fever due to neoplastic disease constitute a relatively constant part of all series. The same can be said for the collagen diseases, in spite of the present great interest in them.

Some Tentative Conclusions

A point deserving emphasis is that most patients with F.U.O. are not suffering from unusual diseases; instead they exhibit atypical manifestations of common illnesses— tuberculosis, sepsis, cancer, blood dyscrasias, pulmonary emboli, rheumatic fever, etc. Furthermore, in the present series of cases delay in diagnosis occasionally resulted because we did not make proper use of available information. Examples of this were our failure to think of brucellosis in an abattoir worker, or of malaria in a man who had visited Panama, or to give sufficient weight to the complaint of dysphagia in a young man with esophageal carcinoma.

The most important lesson we have learned from this study is that, in many instances, attempts to obtain tissue for diagnosis were instituted too late. Many of our patients remained ill for long periods of time, undergoing numerous radiographic examinations and therapeutic trials, while lymph node or liver biopsy was not even under consideration. Procrastination in obtaining tissue for diagnosis is particularly blameworthy when there are palpably enlarged organs and masses. Sutton's Law* needs to be kept in mind by the diagnostician.

A possible exception to the principle of Sutton's Law is found in the procedure of needle biopsy of the liver. Liver tissue is likely to reflect the presence of many systemic diseases, and biopsy was of great value to us in the diagnosis of neoplasms, tuberculosis, sarcoidosis and granulomatous hepatitis, even when the liver was not enlarged and function tests were normal.

When facilities for liver biopsy are not available, laparotomy and open biopsy should be given serious consideration. Geraci *et al.* (91) described 70 patients with F.U.O., only 30 of whom had signs or symptoms referable to the abdomen, who were subjected to laparotomy. In 80 per cent of these abdominal exploration provided the diagnosis. While needle biopsy of the liver might have sufficed in many of their cases, several instances of localized abscess, retroperitoneal tumor and tuberculous peritonitis would have been missed. The importance of laparotomy to establish the diagnosis of tuberculous peritonitis has been emphasized by Bennett (94).

We believe that laparotomy should be performed in most jaundiced patients with long-continued high fever of uncertain origin. All of our patients in that category had intra-abdominal or liver abscesses, or obstructive disease of the biliary tract; nevertheless liver biopsy showed only mild cholangitis. Under these circumstances exploratory laparotomy not only led to correct diagnosis, but sometimes also to a curative procedure. The problem is particularly

TABLE V

Diagnostic Categories in Various Case Series

Authors	Hamman, Wainwright	Keefer	Bottiger	Geraci *et al*	Petersdorf, Beeson
Year	1936	1939	1953	1959	1960
Number of cases	54	75	34	70	100
Percentage of:					
Infections	59	65	46	24	36
Tuberculosis	17	11	17	7	11
Pyogenic	20	49	20	13	22
Other	22	5	9	4	3
Neoplastic diseases	23	20	30	30	19
Carcinoma	15	13	24	16	11
Lymphoma	7	7	6	14	8
Collagen disorders	0	11	12	8	15
Miscellaneous	0	4	12	24	23
No diagnosis made	19	0*	0*	14	7

* Not included in analysis

* We are indebted to Dr. William Dock for the term Sutton's Law. It recommends proceeding immediately to the diagnostic test most likely to provide a diagnosis, and deplores the tendency to carry out a battery of "routine" examinations in conventional sequence. The derivation of the term is as follows: When Willie Sutton, a hold-up man, was being interviewed by newsmen he was asked why he always robbed banks. Sutton, with some surprise, replied, "Why, that's where the money is."

difficult in patients with cirrhosis. Tisdale has recently reviewed 150 cases of Laennec's cirrhosis and found that more than half of these exhibited fever at some time (95). In about 70 per cent of instances the elevation in temperature could be attributed to the cirrhotic process, but among the remainder were several who required surgical treatment.

At the present time it is difficult to refrain from treating the patient with F.U.O. with various antibiotics in the hope that he may have bacterial endocarditis, brucellosis, pyelonephritis, cryptic sepsis, tuberculosis, and the like. At least 90 per cent of our patients had received one or more courses of antimicrobials. This sometimes led to confusion by transient suppression of signs and symptoms, or the appearance of drug fever. We do not mean to imply that therapeutic trials do not have a place in the management of such cases; on the contrary, judicious use of aspirin in rheumatic fever, specific chemotherapeutics such as chloroquine, emetine, penicillin, isoniazid and arsenic, and occasionally even cortisone, heparin or nitrogen mustards may be of value in diagnosis and treatment. However, we believe that in most cases therapeutic trials should be postponed until rational methods of diagnosis have been tried.

No patient with prolonged pyrexia should be subjected to a "routine" battery of laboratory tests, x-rays and biopsies. Each must be evaluated individually. We believe, however, that the quest should be a vigorous one, since in many instances the patient can be helped. In our group of cases nearly two-thirds of the patients recovered or improved, or could be helped to "live with" their disease, because positive diagnosis had provided more accurate knowledge of the future course.

REFERENCES

1. Wunderlich, C. A.: On the temperature in diseases. London, New Sydenham Society, 1871.
2. Hamman, L. and Wainwright, C. W.: Diagnosis of obscure fever. Bull. Johns Hopkins Hosp. **58:** 109 and 307, 1936.
3. Reimann, H. A.: Habitual hyperthermia. J. Amer. Med. Assn. **99:** 1860, 1932.
4. Chapman, C. B. and Whorton, C. M.: Acute generalized miliary tuberculosis in adults. New Eng. J. Med. **235:** 239, 1946.
5. Saphir, O.: Changes in the liver and in the pancreas in chronic pulmonary tuberculosis. Arch. Path. **7:** 1026, 1929.
6. Terry, R. B. and Gunnar, R. M.: Primary miliary tuberculosis of the liver. J. Amer. Med. Assn. **164:** 150, 1957.
7. Harvey, A. M. and Whitehill, M. R.: Tuberculous pericarditis. Medicine **16:** 45, 1937.
8. Sanford, J. P. and Favour, C. B.: The interrelationships between Addison's disease and active tuberculosis; a review of 125 cases of Addison's disease. Ann. Int. Med. **45:** 56, 1956.
9. Fisher, H. C. and White, H. M., Jr.: Biliary tract disease in the aged. Arch. Surg. **63:** 536, 1951.
10. MacGregor, G. A.: Murmurless bacterial endocarditis. Brit. Med. J. **1:** 1011, 1956.
11. Simeone, F. A.: Perinephric abscess. Arch. Surg. **45:** 424, 1942.
12. Schreiner, G. E.: The clinical and histologic spectrum of pyelonephritis. Arch. Int. Med. **102:** 32, 1958.
13. Spink, W. W., Hoffbauer, F. W., Walker, W. W. and Green, R. A.: Histopathology of the liver in human brucellosis. J. Lab. and Clin. Med. **34:** 40, 1949.
14. Whipple, R. L. and Harris, J. F.: B. coli septicemia in Laennec's cirrhosis of the liver. Ann. Int. Med. **33:** 462, 1950.
15. Martin, W. J., Spittel, J. A., Morlock, C. G. and Baggenstoss, A. H.: Severe liver disease complicated by bacteremia due to Gram-negative bacilli. Arch. Int. Med. **98:** 8, 1956.
16. Caroli, J. and Platteborse, R.: Septicémie porto-cave. Cirrhoses du foie et septicémie a colibacille. Sem. hôp. Paris **34:** 472, 1958.
17. Horder, T. and Gow, A. E.: Psittacosis; record of 9 cases with special reference to morbid anatomy in 2 of them. Lancet **1:** 442, 1930.
18. Seibert, R. H., Jordan, W. S. Jr. and Dingle, J. H.: Clinical variations in the diagnosis of psittacosis. New Eng. J. Med. **254:** 925, 1956.
19. Briggs, L. H.: The occurrence of fever in malignant disease. Am. J. Med. Sci. **166:** 846, 1923.
20. Abrams, H. L., Spiro, R. and Goldstein, N.: Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer **3:** 74, 1950.
21. Wintrobe, M. M.: Clinical Hematology. 4th Edition, Lea and Febiger, Philadelphia, 1956, pp. 248–250.
22. Isaacson, N. H. and Rapaport, P.: Eosinophilia in malignant tumors: its significance. Ann. Int. Med. **25:** 893, 1946.
23. Bell, E. T.: Carcinoma of the pancreas. I. A clinical and pathologic study of 609 necropsied cases. Am. J. Path. **33:** 499, 1957.
24. Cliffton, E. E.: Carcinoma of the pancreas. Am. J. Med. **21:** 760, 1956.

25. Berlin, D. A. and Porter, W. B.: Fever: a common symptom of carcinoma of the stomach. Virginia Med. Monthly **77:** 59, 1950.
26. Hartmann, H.: Intermittierende, Malaria ähnliche Fieberparoxysmen bei Magenkarzinomen. Deutsche Klin. Wchnschr. **75:** 1153, 1955.
27. Shedd, D. P., Crowley, L. G. and Lindskog, G. E.: A 10 year study of carcinoma of the esophagus. Surg., Gynec. and Obs. **101:** 55, 1955.
28. Merendino, D. A. and Mark, V. H.: Analysis of 100 cases of squamous-cell carcinoma of esophagus; with special reference to delay periods and delay factors in diagnosis and therapy, contrasting state and city and county institutions. Cancer **5:** 52, 1952.
29. Willis, R. A.: In Pathology of Tumors, 2nd Ed. C. V. Mosby Co., St. Louis, Mo., pp. 911–913.
30. Steiner, P. E.: Multiple diffuse fibrosarcoma of bone. Am. J. Path. **20:** 877, 1944.
31. Aisner, M. and Hoxie, T. B.: Bone and joint pain in leukemia, simulating acute rheumatic fever and subacute bacterial endocarditis. New Eng. J. Med. **238:** 733, 1948.
32. Berger, L. and Sinkoff, M. W.: Systemic manifestations of hypernephroma: a review of 273 cases. Am. J. Med. **22:** 781, 1957.
33. Greenburg, D.: Obscure fever caused by carcinoma of the kidney; a possible explanation for difficulties in diagnosis. Arch. Int. Med. **90:** 395, 1952.
34. Plimpton, C. A. and Gellhorn, A.: Hypercalcemia in malignant disease without evidence of bone destruction. Amer. J. Med. **21:** 750, 1956.
35. Hempstead, R. H. and Priestly, J. T.: Fever as a predominant symptom of hypernephroma: report of two cases. Proc. Staff Meet. Mayo Clin. **27:** 67, 1952.
36. Bloomer, W. E. and Lindskog, G. E.: Bronchogenic carcinoma. A report comparing three consecutive series of 100 cases each. Cancer **4:** 1171, 1951.
37. Melicow, M. M.: Primary tumors of the retroperitoneum. J. Internat. Coll. Surgeons, **19:** 401, 1953.
38. Bottiger, L. E.: Fever of unknown origin. II. A discussion around four typical cases. Acta med. scand. **154:** 215, 1956.
39. Sinn, C. M. and Dick, F. W.: Monocytic leukemia. Amer. J. Med. **20:** 588, 1956.
40. Meacham, G. C. and Weisberger, A. S.: Early atypical manifestations of leukemia. Ann. Int. Med. **41:** 789, 1954.
41. Silver, R. T., Utz, J. P., Frei, E. III and McCullough, N. B.: Fever, infection and host resistance in acute leukemia. Amer. J. Med. **24:** 25, 1958.
42. Jones, T. D.: The diagnosis of rheumatic fever. J. Amer. Med. Assn. **126:** 481, 1944.
43. Ferris, E. B. Jr. and Myers, W. K.: Initial attacks of rheumatic fever in patients over 60 years of age. Arch. Int. Med. **55:** 809, 1935.
44. Grifone, J. W. and Kitchell, J. R.: Active rheumatic heart disease in patients over sixty. J. Amer. Med. Assn. **154:** 1341, 1954.
45. Harvey, A. McG., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H.: Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Med. **33:** 291, 1954.
46. Sagall, L. E., Bornstein, J. and Wolff, L.: Clinical syndrome in patients with pulmonary embolism. Arch. Int. Med. **76:** 234, 1945.
47. Chapman, J. S.: Pulmonary infarction. So. Med. J. **45:** 597, 1952.
48. Thomas, W. A., Randall, R. V., Bland, E. F. and Castleman, B.: Endocardial fibroblastosis: a factor in heart disease of obscure etiology. New Eng. J. Med. **251:** 327, 1954.
49. Cohn, A. E. and Steele, N. J.: Unexplained fever in heart failure. J. Clin. Invest. **13:** 853, 1934.
50. Petersdorf, R. G. and Merchant, R. K.: A study of antibiotic prophylaxis in patients with acute heart failure. New Eng. J. Med. **260:** 565, 1959.
51. Gerber, I. E. and Mendlowitz, M.: Visceral thrombophlebitis migrans. Ann. Int. Med. **30:** 560, 1949.
52. Alexander, H. L.: In Reactions with Drug Therapy. Philadelphia, W. B. Saunders Co., 1955, pp. 49–65.
53. Clarkson, B. H., Goldberg, B. L. and Segal, J. P.: Dilantin sensitivity. Report of a case of hepatitis with jaundice, pyrexia and exfoliative dermatitis. New Eng. J. Med. **242:** 897, 1950.
54. More, R. H., McMillan, G. C. and Duff, L. G.: The pathology of sulfonamide allergy in man. Am. J. Path. **22:** 703, 1946.
55. Maisel, B., McSwain, B. and Glem, F.: Effects of administration of sodium sulfadiazine in dogs. Arch. Surg. **46:** 326, 1943.
56. Dressler, W.: A post-myocardial-infarction syndrome. J. Amer. Med. Assn. **160:** 1379, 1956.
57. Levy, R. L. and Patterson, M. C.: Acute serofibrinous pericarditis of undetermined cause. A study of 27 cases. Am. J. Med. **8:** 34, 1950.
58. Gelfand, M. L. and Goodkin, L.: Acute benign nonspecific pericarditis without a pericardial friction rub. Ann. Int. Med. **45:** 490, 1956.

59. LONGCOPE, W. T. AND FREIMAN, D. G.: A study of sarcoidosis. Medicine **31**: 1, 1952.
60. COWDELL, H.: Sarcoidosis: with special reference to diagnosis and prognosis. Quart. J. Med. **23**: 29, 1954.
61. LOFGREN S.: Primary pulmonary sarcoidosis. I. Early signs and symptoms. Acta med. Scand. **145**: 424, 1953.
62. LOFGREN, S.: Primary pulmonary sarcoidosis. II. Clinical course and prognosis. Acta med. Scand. **145**: 465, 1953.
63. PLATTS, M. M. AND GREAVES, M. S.: Splinter hemorrhages. Brit. Med. J. **2**: 143, 1958.
64. BIRKENHEAD, N. C., WAGENER, H. P. AND SHICK, R. M.: Treatment of temporal arteritis with adrenal corticosteroids: results in 55 cases in which lesion proved at biopsy. J. Amer. Med. Assn. **163**: 821, 1957.
65. REIMANN, H. A.: Regularly periodic fever of eleven years' duration. Acta. med. Scand. **196**: 666, 1947.
66. REIMANN, H. A.: Periodic disease. Medicine **30**: 219, 1951.
67. KAPPAS, A., HELLMAN, L., FUKUSHIMA, D. AND GALLAGHER, T. F.: The pyrogenic effect of etiocholanolone. J. Clin. Endocrinol. **17**: 451, 1957.
68. BONDY, P. K., COHN, G. L., HERRMANN, W. AND CRISPELL, K. R.: The possible relationship of etiocholanolone to periodic fever. Yale J. Biol. and Med. **30**: 395, 1958.
69. HELLER, H., SOHAR, E. AND SHERF, L.: Familial Mediterranean fever. Arch. Int. Med. **102**: 50, 1958.
70. PRIEST, R. J. AND NIXON, R. K.: Familial recurring polyserositis: a disease entity. Ann. Int. Med. **51**: 1253, 1959.
71. HALLAHAN, J. D. AND KLEIN, T.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease). Ann. Int. Med. **34**: 1179, 1951.
72. WERNER, S. C.: Thyroiditis in "The Thyroid." New York, Paul B. Hoeber, 1955.
73. CRILE, G., JR. AND RUMSEY, E. W.: Subacute thyroiditis. J. Amer. Med. Assn. **142**: 458, 1950.
74. MAYER, L.: Die Wunden der Milz. Leipzig, F. C. W. Vogel, Verlag, 1878.
75. LABREE, R. H., FULLER, J. AND BOMAN, P. G.: Spontaneous rupture of the spleen after acute pancreatitis. J. Amer. Med. Assn. **172**: 816, 1960.
76. RICHMAN, A.: Acute pancreatitis. Amer. J. Med. **21**: 246, 1956.
77. LEONARD, B. J., ISRAELS, M. C. G. AND WILKINSON, J. F.: Myelosclerosis. Quart J. Med. **26**: 131, 1957.
78. KORST, D. R., CLATANOFF, D. V. AND SCHILLING, R. F.: On myelofibrosis. Arch. Int. Med. **97**: 169, 1956.
79. CRAIL, H. W., ALT, H. L. AND NADLER, W. H.: Myelofibrosis associated with tuberculosis. Blood **3**: 1426, 1948.
80. PETERSDORF, R. G. AND BENNETT, I. L., JR.: Factitious fever. Ann. Int. Med. **46**: 1039, 1957.
81. DUBOIS, E. F.: Why are fever temperatures ove 106 F. rare? Am. J. Med. Sci. **217**: 361, 1949.
82. STROBER, M.: Fever of undetermined origin: presumptive cause, amebic colitis. U. S. Armed Forces Med. J. **7**: 1055, 1956.
83. SHUBERT, S., COLLEE, J. G. AND SMITH, B. J.: Infectious mononucleosis—a syndrome or a disease? Brit. Med. J. **1**: 671, 1954.
84. BEVERLY, J. K. A. AND BEATTY, C. P.: Glandular toxoplasmosis. Survey of 30 cases. Lancet **2**: 379, 1958.
85. BARONDESS, J. A.: Thrombotic thrombocytopenic purpura. Amer. J. Med. **13**: 294, 1952.
86. ADELSON, E., HEITZMAN, E. J. AND FENNESSY, J. F.: Thrombohemolytic thrombocytopenic purpura. Arch. Int. Med. **94**: 42, 1954.
87. ALT, H. L. AND BARKER, H.: Fever of unknown origin. J. Amer. Med. Assn. **94**: 1457, 1930.
88. KINTNER, A. R. AND ROWNTREE, L. G.: Long-continued, low-grade, idiopathic fever. Analysis of 100 cases. J. Amer. Med. Assn. **102**: 889, 1934.
89. KEEFER, C. S.: The diagnosis of the causes of obscure fever. Texas State J. Med. **35**: 203, 1939.
90. BOTTIGER, L. E.: Fever of unknown origin. With some remarks on the normal temperature in man. Acta med. Scand. **147**: 133, 1953.
91. GERACI, J. E., WEED, L. E. AND NICHOLS, D. R.: Fever of obscure origin—the value of abdominal exploration in diagnosis. Report of 70 cases. J. Amer. Med. Assn. **169**: 1306, 1959.
92. FINLAND, M., JONES, W. F., JR. AND BARNES, M. W.: Changes in the occurrence of serious bacterial infections since the introduction of antibacterial agents. Tr. Assn. Amer. Phys. **72**: 305, 1959.
93. Editorial: Prevalence of tuberculosis in large cities. J. Amer. Med. Assn. **157**: 512, 1955.
94. BENNETT, I. L., JR.: A consideration of fever of undetermined origin. J. Med. Assn. Georgia **45**: 389, 1956.
95. TISDALE, W. A.: Personal communication.