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Fever in Neoplastic Disease

Samuel L. Rosenthal, M.D.* and Robert W. Talley, M.D.**

A comparison is made between incidence of fever in 132 patients with various types of disseminated cancer and 57 patients with diseases other than cancer during a 2-month observation period. Fifty-three febrile episodes were observed in cancer patients. Of these, 15 were of undetermined origin and 6 were noninfectious; none of the episodes occurred immediately following surgery. In the control group of 57 patients, there were 12 febrile episodes; of these, 7 were due to proven bacterial infection, 2 were due to possible bacterial infection, and 3 were of undetermined etiology. All three febrile episodes in this latter group occurred postoperatively. The pathogenesis of fever is discussed, especially unexplained fever, in the absence of infection. Tissue necrosis, with the release of endogenous pyrogen, is suggested as a pathogenic mechanism in neoplastic fevers. It is of interest that unexplained fever was more prevalent in patients with demonstrable liver metastases. The metabolism of naturally occurring steroid hormones may be impaired by hepatic dysfunction. The role of steroid pyrogens remains undefined. Hepatic dysfunction may be a contributory factor.

Although it is well-known that fever may occur in association with neoplastic diseases, few attempts have been made to determine the etiology of neoplastic fevers.¹ Boggs and Frei² studied the fever in 127 patients with neoplastic disease. All but 30 patients had either leukemia or lymphoma. Eighty-six patients had 193 febrile episodes; 173 were inadequately evaluated. Infection was noted in 44% of these 173 febrile episodes. The authors concluded that the remaining 56% had "fever of undetermined origin." Browder, Huff, and Petersdorf³ studied 343 patients with neoplastic disease. The majority of their patients had either carcinoma or sarcoma; only 2 had acute leukemia. Two hundred forty-one had 249 bouts of fever, which were attributed to infection or intestinal obstruction in 189 episodes (76%). In approximately two-thirds of these cases, the infection or obstruction was

attributed to the presence of tumor. The authors felt that only 19 episodes of fever were caused by tumor. The remaining 41 cases were felt to have been evaluated insufficiently. In reviewing the results of Boggs and Frei, Browder et al pointed out that their own series included only a few patients with leukemia and lymphoma.

In the "fevers of undetermined origin" described by Boggs and Frei, 77 of 97 occurred in patients with either acute leukemia or Hodgkin's disease. The high incidence of cryptogenic fever in Hodgkin's disease was confirmed by the work of Lobell, Boggs and Wintrobe.⁴ They found evidence of bacterial infection in 13% of febrile patients with Hodgkin's disease and no evidence of infection in 50%. However, in two series of patients with acute leukemia^{5,6} approximately two-thirds of febrile episodes were attributed to infection.

In patients with carcinoma or sarcoma, fever unaccompanied by infec-

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tion has been reported to occur frequently, especially when hepatic metastases are present. Fenster and Klatskin⁷ found such fevers in 19 of 81 patients with proven hepatic metastases.

The present study was undertaken in order to investigate the incidence and causes of febrile episodes in patients on the Henry Ford Hospital Oncology service. The relationship of fever to the presence of hepatic metastases was examined as well.

Materials and Methods

One hundred thirty-two patients with neoplastic diseases were studied during February and March, 1969. These included all of the patients on the Henry Ford Hospital Oncology service, who were hospitalized in its principal inpatient ward, and the patients of the "X-Division" elsewhere in the hospital. All patients included in the study had a single type of histologically-proved malignancy which was not surgically resectable. Twelve of the patients were seen during more than one hospital admission. The majority of patients had neoplasms of epithelial origin (Table I). Twenty patients had reticuloendothelial system tumors and one patient had chronic lymphocytic leukemia. There were no cases of acute leukemia. The youngest patient was 18 years old and all but two were 21 years or older.

A control group of patients with diseases other than cancer was studied. This group consisted of 57 patients admitted for treatment of a variety of illnesses in the Oncology service ward, primarily because of the availability of beds. This group cannot be called a strict control group because the seriousness of illness, length of hospitaliza-

Table I

<u>Diagnoses of Patients with Neoplastic Disease</u>	
Carcinoma	99
Sarcoma	7
Melanoma	6
Multiple Myeloma	4
Lymphoma	16
Lymphosarcoma	5
Hodgkin's Disease	4
Reticulum Cell Sarcoma	6
Chronic Lymphocytic Leukemia	1
Total	132

tion, and age distribution of patients were dissimilar to those with neoplastic disease. However, the choice of these patients selected for comparison was truly random, and provided a good cross-section of noncancer patients admitted to a general hospital.

All patients were followed for at least four days from the day of admission and four days from the first observation of an elevated temperature. A febrile episode was defined by the presence of one or more of the following criteria:

1. oral or rectal temperature of 101 F (38.3 C) or higher on more than one determination on any day;
2. temperature of 100 F (37.8 C) or higher on two consecutive days;
3. temperature of 100 F (37.8 C) on three of any seven consecutive days.

A febrile episode was defined as terminated if the last febrile day was followed by at least seven days during which the temperature was less than 100 F (37.8 C).

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All patients were interviewed and examined at the time when a febrile episode occurred. If no source of fever was apparent, patients with temperature elevations below 101 F (38.3 C) were usually observed for several days before further diagnostic studies were performed. Patients with persistent or marked temperature elevation of undiagnosed source were investigated with chest roentgenograms, blood count, urine culture, and at least two blood cultures. Cultures of sputum, stool, and drainage from wounds and fistulas were also obtained as indicated. Fever was considered due to infection if an apparent source of infection was found on examination and if one of the following conditions existed:

1. the temperature returned to normal as the signs and symptoms of infection receded;
2. the temperature promptly returned to normal with the institution of appropriate antibiotic therapy as indicated by cultures;
3. blood cultures were positive on more than one occasion;
4. a significant infection was found at autopsy.

A patients was said to have a fever of undetermined origin if:

1. no apparent source of fever was found on interview and examination, including roentgenographic examination;
2. the temperature returned to normal without specific treatment and all studies were negative;
3. no evidence of infection was found at autopsy performed within three days of a febrile day.

Results

Eighty-one patients with neoplastic disease (60%) had no febrile episodes during the period of observation; 53 patients (40%) did (Table II). Twenty-three of the febrile episodes met the criteria for fever of infection. The types of infection encountered are listed in Table III. Nine additional patients may also have had infection. Three of these had a prompt deferescence when started on antibiotics and subsequent cultures were all negative. Three patients had bacteriological evidence of infection but were not treated. Two patients had single positive blood cultures prior to death and

Table II
Classification of Fevers

Patients in Group	All Patients with Cancer		Patients with Proven Liver Metast.		Patients with no Proven Liver Metast.		Liver Metast. Undeterm.		Control Group	
	132		26		45		61		57	
Patients with Fever	53	40.1%	15	57.7%	12	26.6%	26	42.6%	12	21.0%
Proven Infection	23	17.4%	3	11.5%	6	13.3%	14	22.9%	7	12.2%
Possible Infection	9	6.8%	4	15.3%	0	--	5	8.2%	2	3.3%
Identifiable Fever of Noninfectious Origin	6	4.5%	1	3.8%	1	2.2%	4	6.5%	0	--
Fever of Undetermined Origin	15	11.3%	7	26.9%	5	11.1%	3	4.9%	3	5.3%

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Table III

Types of Infection Among Patients With Neoplastic Disease

Urinary Tract Infection	6
Pneumonia	3
Postoperative Wound Infection	3
Upper Respiratory Infection	3
Septicemia	1
Lung Abscess	1
Empyema	1
Bacterial Enteritis	1
Liver Abscess	1
Bacterial Otitis	1
Infected Fistulous Tract in Region of Tumor	2
Total	23

autopsies were not performed. The chest roentgenograms of one patient in this group showed collapse of the left lower lobe.

Six patients had fever due to identifiable causes other than infection. Three were felt to have had febrile reactions to medications. An additional patient developed fever after injection of lipiodol for a lymphangiogram. One patient suffered severe colitis following radiotherapy to the abdomen. Stool cultures were negative. Her temperature returned to normal as diarrhea subsided. One patient had chest pain, diaphoresis and an unstable EKG pattern suggesting myocardial damage as the etiology of febrile episode.

Fever of undetermined origin occurred in 15 patients (28% of febrile episodes). Eleven of these patients had carcinoma, two had lymphoma, and one each had melanoma and sarcoma. Six patients had brief bouts of fever lasting from two to seven days followed by afebrile periods which lasted until the time of discharge or death. Four had intermittent, irregularly spaced low-grade temperature elevations. One patient was released from the hospital

after one week of sustained low-grade fever when cultures and skin test and sputum smear for tuberculosis were all negative. The remaining four patients had daily temperature elevations throughout their long hospital courses. Their diagnoses were: Hodgkin's disease, reticulum cell sarcoma, carcinoma of the rectum, and leiomyosarcoma of the uterus. Investigation in all included multiple blood and urine cultures as well as cultures for acid-fast bacilli. Two of the patients died and autopsy revealed no evidence of infection.

Twenty-six patients had definite evidence of hepatic metastases; in 13, hepatic involvement was seen at laparotomy or autopsy; in three, malignant cells were found on liver biopsy. The remaining 10 patients had both abnormal liver chemistries and evidence of hepatic metastases on liver scan, thorotrast hepatogram, or hepatic arteriogram. The incidence of fever of undetermined origin and the total incidence of fever was higher in this group as a whole than in a group of patients with neoplastic disease. Seven (28%) of this small group had fever of undetermined origin (Table II). This is quite similar to the 23% observed by Fenster and Klatskin.⁷

Of the remaining 106 patients, 45 had had sufficient studies to rule out hepatic metastases definitely. In five of these no evidence of hepatic involvement was seen at autopsy while in the remaining 40, physical examination of the liver was negative, the SGOT was less than 40 units, and BSP retention was less than 5% at 45 minutes. The overall incidence of fever was less in this group than in the total group although the incidence of fever of un-

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determined origin was similar (Table II).

The control group of patients had proportionately fewer bouts of fever than the cancer patients although this may be explainable in part by their shorter average hospital stay. Three patients had fever of undetermined origin. All three had brief episodes of low-grade temperature elevation in an immediate postoperative period. The temperature returned to normal within three days and thus was not investigated further. If postoperative fever is excluded, the incidence of fever of undetermined origin in the group of patients who had no neoplastic disease was zero. None of the episodes of fever of undetermined origin among the cancer patients occurred immediately following surgery.

Discussion

The results presented here confirm the fact that fever occurs frequently in patients with cancer and probably is more prevalent than in other hospitalized patients on medical service. Unexplained fever is common in patients with neoplastic disease while it is encountered rarely in patients who are hospitalized for other reasons. No evidence of bacterial infection was found in 28% of febrile episodes noted in patients with malignancies. This figure lies between the 56% reported by Boggs and Frei² and the 7.6% observed by Browder et al.³ The work of Fenster and Klatskin⁷ was confirmed in that fever of undetermined origin was found more often in patients with hepatic metastases than in the group as a whole.

The common denominator in many of the above cases of unexplained fever

may be tumor necrosis. Animal experiments have shown that necrotic tumor tissue may be pyrogenic.⁸ This may be due to the attraction of leukocytes to necrotic tissue and their subsequent breakdown with the release of endogenous pyrogen.⁹ However, fever may occur in the presence of leukopenia,⁹ and endogenous pyrogen has been recovered from many tissues other than leukocytes.¹⁰ Thus necrosis of tumor tissue or the destruction of adjacent normal tissue by a rapidly growing tumor may, in itself, cause the release of pyrogen. It is easy to imagine such a mechanism as the cause of brief, isolated, or intermittent bouts of fever. Similarly, tissue destruction with or without involvement of leukocytes may well have been important in the pathogenesis of the three postoperative "fevers of undetermined origin" that occurred in the comparison group.

It is more difficult to rationalize the prolonged and persistent unexplained fever that occurred in four patients. No evidence of infection or necrotic tissue was found when autopsies were performed on two of the patients. At the end of the study, the other two patients were living, and occult infection and continuing tissue necrosis are possibilities. Endogenous pyrogen can be released under the influence of certain steroid hormones.¹¹ One can only speculate about the role of such hormones in the pathogenesis of fever in these four patients with tumors of widely varying histological types: ie, Hodgkin's disease, reticulum cell sarcoma, carcinoma, and leiomyosarcoma.

Several theories have been advanced to explain the increased incidence of unexplained fever in patients with he-

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patic metastases. Lithocholic acid, a 3 α -mono-hydroxysteroid, has been found to be the only free C-24 bile sterol that was pyrogenic in man.¹² Thus, interference with the metabolism of bile sterols has been suggested as a mechanism.¹³ Also, the metabolism of naturally occurring steroid hormones may be impaired in the presence of hepatic dysfunction.¹³ In addition, interference with the reticuloendothelial functions of the liver may impede the removal of pyrogenic substances from the circulation. However, the prominence of fever as a symptom in these patients may simply reflect the fact that demonstrable hepatic metastases tend to occur in patients with advanced disease. In the present series, there were 11 deaths among the 26 patients who were thought to have liver involvement; while only 8 of the 45 patients, who had no evidence of hepatic metastases, died.

Summary

During a two-month period of observation of hospitalized patients in the wards of an Oncology service, 53 febrile episodes occurred among 132 patients. In 15 of the episodes (28%) no apparent cause could be found. The incidence of unexplained fever and the total incidence of fever were both higher in patients with cancer than in a group of patients who did not have cancer. Unexplained fever occurred more frequently in patients with demonstrable hepatic metastases than in those who did not have hepatic metastases. Tissue necrosis, with the release of endogenous pyrogen, may be an important pathogenic mechanism in neoplastic fevers, particularly in brief or intermittent episodes. The role of steroid pyrogens remains undefined. Hepatic dysfunction may be a contributing cause.

REFERENCES

1. Silver, R. T.: Infections, fever and host resistance in neoplastic diseases, *J Chronic Dis* 16: 677-701, Jul 1963.
2. Boggs, D. R., and Frei, E., III: Clinical studies of fever and infection in cancer, *Cancer* 13:1240-53, Nov-Dec 1960.
3. Browder, A. A.; Huff, J. W.; and Petersdorf, R. G.: The significance of fever in neoplastic disease, *Ann Intern Med* 55:932-42, Dec 1961.
4. Lobell, M.; Boggs, D. R.; and Wintrobe, M. M.: The clinical significance of fever in Hodgkin's disease, *Arch Intern Med* 117:335-42, Mar 1966.
5. Raab, S. O., et al: The clinical significance of fever in acute leukemia, *Blood* 16:1609-28, Nov 1960.
6. Silver, R. T., et al: Fever, infection, and host resistance in acute leukemia, *Amer J Med* 24:25-39, Jan 1958.
7. Fenster, L. F., and Klatskin, G.: Manifestations of metastatic tumors of the liver, *Amer J Med* 31:238-48, Aug 1961.
8. Allen, I. V.: The relationship of fever to tumour necrosis in the rat, *Brit J Cancer* 18:378-85, Jun 1964.
9. Atkins, E.: Pathogenesis of fever, *Physiol Rev* 40:580-646, Jul 1960.
10. Snell, E. S., and Atkins E.: The presence of endogenous pyrogen in normal rabbit tissues, *J Exp Med* 121:1019-38, Jun 1965.
11. Bodel, P. T.; Dillard, M.; and Bondy, P. K.: The mechanism of steroid-induced fever, *Ann Intern Med* 69:875-9, Nov 1968.
12. Palmer, R. H.; Glickman, P. B.; and Kappas, A.: Bile acid fever and inflammation in man, abstracted in *J Clin Invest* 40:1069, Jun 1961.
13. Beaty, H. N., and Petersdorf, R. G.: Significance of fever in patients with malignant disease, *Geriatrics* 22:139-47, Jan 1967.