Infectious

DRUG FEVER

Medical Grand Rounds

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In the spring of 1986, the Metabolic Unit at the V.A. Hospital consulted the Infectious Diseases Service regarding unexplained fever in a patient participating in their "hyperlipidemia study".

Case report: The patient was a 60 year old caucasian male, admitted to the Metabolic Unit on 4/23/86 for evaluation and treatment of complications relating to long-standing hyperlipidemia, hypertension and hyperuricemia. He had no known allergies and was receiving lasix, slow K, persantin and metoprolol at the time of admission. His initial physicial examination was remarkable for the presence of hypertensive retinopathy and reduced periferal pulses. The patient was afebrile. The serum triglyceride and cholesterol levels were 870 mg% and 253mg%, respectively. An LDL turnover study was initiated on the day of admission with administration of SSKI (3 gtts in water p.o. each day) to block thyroid uptake of I-125 contained in a radioiodinated LDL maker. The radiolabeled LDL was administered on 4/29/86. The evening of 5/4/86, the patient noted the onset of fever and myalgias, and thought he was "coming down with the flu". There was mild leukocytosis at this time but no eosinophilia. Malaise, myalgias and hectic fever (Figure 1) persisted until 5/8/86 when SSKI was discontinued at the suggestion of the Infectious Diseases Service. By the following day, the fever and flu-like symptoms had resolved. On 5/10/86, the patient was rechallenged with SSKI. Within 2 hours, his fever and myalgias returned. No further SSKI was given, and these resolved within 24 hours. Unfortunately, due to poor communication between the Infectious Diseases Service and nursing staff, only a single AM temperature was recorded on the day of the rechallenge. This was recorded as 99.8^{o}F.

In retrospect, the foregoing patient typified the syndrome of drug fever. However many features of his illness also conflicted with descriptions of the clinical condition in textbooks and review articles. Unfortunately, owing to the absence of any comprehensive clinical review of the entity, the validity of these writings had never been tested. In fact, most of what has been written about drug fever appears to have emanated ex cathedra from a small circle of noted infectious diseases clinicians. Not surprisingly, many such writings are vague and/or conflicting.

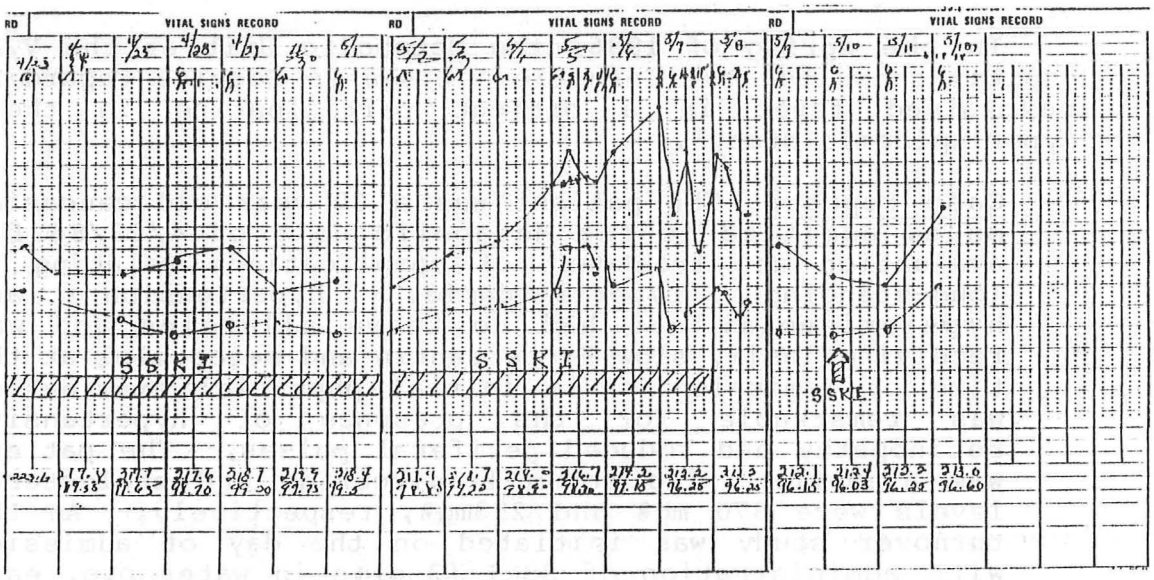

Figure 1. Temperature graph (SSKI-induced fever)

APHORISIMS

The following quotations are representative of the unsubstantiated information on drug fever promulgated in the current literature:

"Fever as the only manifestation of a drug reaction is infrequent..." (1)

"Such reactions may occur more frequently than many physicians realize" (2).

"Patients with drug fever often look relatively well, and commonly have a relatively normal pulse rate during febrile episodes" (3).

"Drug fever is extremely common with certain antimicrobials, particularly penicillin..." (4).

"A drug well tolerated for many years may abruptly induce a reaction, including fever" (5).

"A sustained fever may be the sole evidence of allergy to a drug" (6).

"The vast majority of fevers are associated with some form of cutaneous manifestion " (7).

"A second challenge with the drug is neither necessary [for diagnosis] nor safe" (4).

In this presentation, I will review an analysis of 51 episodes of drug fever diagnosed at Parkland Memorial Hospital or the Dallas V.A.M.C. between 1959 and 1986 and another 97 published case reports. Through this analysis I will attempt to evaluate descriptions of this clinical entity in current textbooks and review articles. I will also review the modest information available on mechanisms responsible for the various forms of drug fever.

DEFINITION

Drug fever is a disorder characterized by fever coinciding with the administration of a drug and disappearing after discontinuation of the drug, when no other cause for the fever is evident after a careful physicial examination and laboratory investigation. As such, drug fever is a diagnosis of exclusion, since no definitive test exists for establishing its existence, and since attempts to confirm the diagnosis by rechallenging subjects have generally been discouraged (4,8). Although I will briefly discuss a wide variety of mechanisms by which drugs may induce fever, most dissertations on the syndrome have been limited to febrile episodes associated with drug-induced hypersensitivity reactions. As such, the neuroleptic malignant syndrome, malignant hyperthermia, the Jarish-Herxheimer reaction, and complications related to drug administration (e.g. phlebitis, chemical meningitis, sterile abscesses, etc.) have not been included in surveys of drug fever.

THERMOREGULATION AND THE FEBRILE RESPONSE

Thermoregulation. Some of the earliest therories of thermoregulation can be traced to the teachings of Hypocrates, who believed that body temperature, and physiological harmony in general, related to a delicate balance between the four humors-- blood, phlegm, black bile and yellow bile (9). Fever was thought to result from an excess of yellow bile, perhaps because at that time, many infections were associated with both fever and jaundice. During the Middle Ages, fever was attributed to demonic possessions requiring exorcism. However, by the 18th century, Harvey's discovery of the circulation of blood and the birth of microbiology led iatrophysicists and iatrochemists to hypothesize alternatively, that body heat and fever resulted from friction associated with the flow of blood through the vascular system and from fermentation and putrefaction occuring in the blood and intestines. Today, thanks to the work of the great French physiologist, Claude Bernard, we recognize that the source of body heat resides in the metabolic processes occuring therein, and that body temperature is rigidly maintained within a narrow range by regulating the rate at which heat generated by these processes is allowed to dissipate from the body.

The body temperature of higher animals is regulated by both physiologic and behavioral means (9,10). The physiologic mechanisms, which distinguish homeotherms (warm-blooded animals) from poikilotherms (cold-blooded animals), are concerned primarily with regulating heat loss by altering the amount of blood brought in contact with the surface of the skin (Figure 2). When excess thermal energy must be released during the thermoregulatory process, circulation to the skin and subcutaneous tissues is increased so that heat exchange with the external environment is potentiated. Sweating increases such heat loss by providing water for vaporization. When thermal energy must be conserved to maintain normal body temperature, then such circulation to surface structures is reduced. When the demand for heat is great, either because the ambient temperature is low or internal requirements are high (e.g. during sepsis),shivering may accompany periferal vasoconstriction as a means of augmenting heat production.

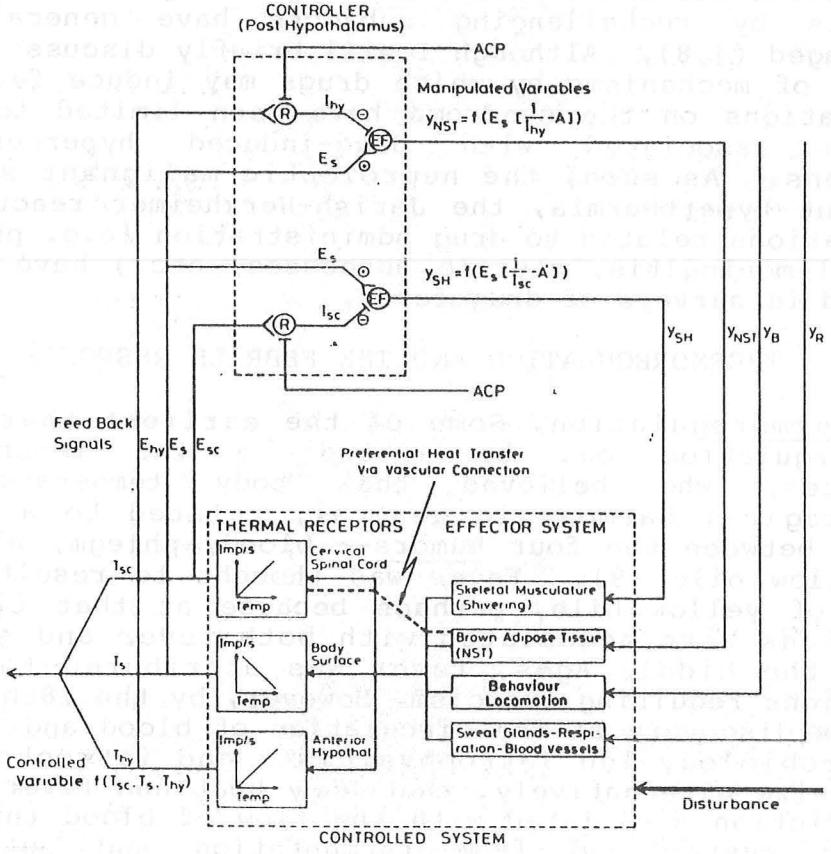

Figure 2. Thermoregulatory pathways.

In higher animals, behavioral responses are also important features of the thermoregulatory response, and represent the only means of thermoregulation in poikilotherms. Humans use behavioral responses, such as moving to heated or air- conditioned rooms, and wearing clothing to augment their physiologic thermoregulatory activities. Such behavioral responses are common during fever, when patients use clothes and blankets to complement physiologic mechanisms serving to raise the body temperature.

The neuronal mechanisms involved in thermoregulation are only partially understood. Although the spinal cord is capable of initiating thermoregulatory responses, the preoptic area of the hypothalamus is the primary site of integration of thermal stimuli, and through its input into the autonomic nervous system, initiation of thermal homeostatic mechanisms. As such, the anterior hypothalamus is the thermal control center responsible for establishing a thermal "set-point" for the body and for coordinating physiological and behavioral responses that bring body temperature in line with that set-point.

The anterior hypothalamus, as well as the skin and spinal cord, contain separate populations of thermally sensitive neurons that respond to either warm or cold stimuli and presumably initiate appropriate thermoregulatory responses to local changes in temperature. Some neurons within the anterior hypothalamus respond only to local temperature changes, while others respond only to those evoked elsewhere in the nervous system. Such variation in neuronal types supports the belief that the hypothalamus is the integrative site of thermoregulation. However, the precise afferent and efferent pathways participating in this process remain to be defined.

Endogenous pyrogen (Interleukin 1). There is little evidence that exogenous pyrogens such as bacteria, viruses or their products cause fever through a direct action on the hypothalamic thermoregulatory center. Rather, the weight of available data favors an indirect effect of such pyrogens on the hypothalamus, that is mediated by "endogenous pyrogens" produced by phagocytic leukocytes (Figure 3).

The existence of a phagocyte-produced pyrexin was first demonstrated in 1948 by Beeson, who extracted a fever-producing substance from rabbit polymorphonuclear leukocytes (11). This substance was shown to be distinct from endotoxin by virtue of its capacity for producing fever of short latency and duration, its heat lability, and its failure to produce pyrogenic tolerance after repeated injection. "Endogenous pyrogen", as the substance is now

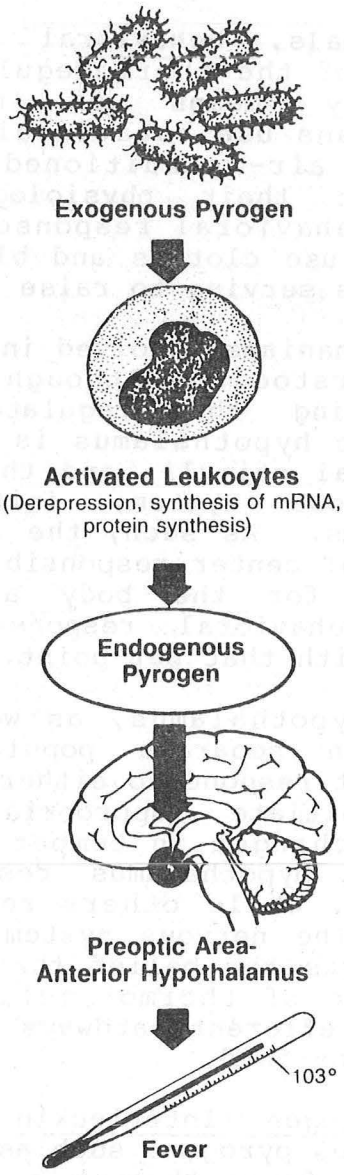

Figure 3. Endogenous pyrogen- mediated fever: physiological pathway.

known, is a low molecular weight protein, produced predominantly by mononuclear phagocytes in response to a diverse group of exogenous pyrogenic stimuli. Spontaneous synthesis and release of endogenous pyrogen has also been documented in human cell lines derived from patients with Hodgkin's disease and histiocytic lymphoma. It is likely that such autonomous synthesis of endogenous pyrogen is the mechanism by which fever develops in association with these malignant neoplasms.

Production of endogenous pyrogen by normal phagocytes appears to involve derepression of a specific genome (11). Following synthesis, the molecule is released without significant storage, and appears to act in the hypothalamus as a calcium ionophore, stimulating arachidonic acid release and thereby synthesis of prostaglandin E2. Although prostaglandin E2 exerts a direct pyrogenic effect on the hypothalamic thermoregulatory center, controversy persists as to whether this effect is essential for the febrile response, or whether endogenous pyrogen acts through some other process requiring protein synthesis.

Early investigations of endogenous pyrogen concentrated on its capacity to cause hyperthermia. In recent years, however, it has become increasingly apparent that this small protein has a wide array of biological activities (12). Prominent among these is its capacity for immune simulation--a capacity reflected by a host of synonyms (Table 1), of which interleukin 1 is the most notable. The biological activities attributed to endogenous pyrogen (Table 2) are also numerous and raise the possibility that it actually represents a family of closely related molecules.

Table 1. Synonyms and acronyms of endogenous pyrogen

Synonym	Acronym
Interleukin 1	IL 1
Leukocyte endogenous mediator	LEM
Lymphocyte activating factor	LAF
B cell activating factor	BAF
Mononuclear cell factor	MCF

Table 2. Examples of biological activities attributed to endogenous pyrogen

Fever	Muscle proteolysis
Hypoferremia	Fibroblast proliferation
Hypozincemia	↑ PGE_2 production
Hypercupremia	↑ Hepatic albumin synthesis
Leukocytosis	↑ Lipoprotein lipase activity
↑ Hepatic acute-phase proteins	

Although fever is a normal response of most higher animals to infection and certain other disease processes, the capacity to mount a febrile response may be impaired in some animals as a result of age or underlying disease. The newborn, the elderly and the severely debililated have long been recognized as having impaired febrile responses to infection. Neonatal homeotherms do not develop fever when injected with pyrogens, but when given an opportunity to select their preferred position in a thermally graded environment, choose warmer positions than control animals. The failure of neonatal animals and their aged counterparts to develop fever in response to exogenous pyrogens appears to reflect an impaired hypothalamic responsiveness, rather than an inability to generate endogenous pyrogen.

Hyperthermia not mediated by endogenous pyrogen. As indicated above, fever is a complex physiologic process, mediated by the action of endogenous pyrogen on the anterior hypothalamus and characterized by a regulated rise in body temperature. There are also a number of febrile disorders in which endogenous pyrogen does not appear to play a role (Table 3). The hyperthermia accompanying these disorders differs from that occurring in classic fever, because it is unregulated (temperature exceeds the thermoregulatory "set-point"), not defended by physiologic mechanism, and does not respond to standard antipyretic agents.

Table 3. Febrile disorders not mediated by endogenous pyrogen.

Fever due to increased heat production:	
Exercise-induced hyperthermia	Malignant hyperthermia
Thyrotoxicosis	Neuroleptic malignant syndrome
Pheochromocytoma	
Fever due to decreased heat dissipation:	
Heat stroke	Dehydration
Drug-induced (e.g. atropine)	Occlusive dressings
Autonomic dysfunction	
Hypothalamic disorders (rare)	
Infections (e.g. granulomas)	Vascular accidents
Tumors	Drug-induced (e.g. phenothiazine)
Trauma	

MECHANISM OF DRUG FEVER

Administration problems. Phlebitis, sterile abscesses, and aseptic meningitis are potential complications of intravenous, intramuscular and intrathecal injections, respectively. Some drugs are notoriously irritating in this regard (e.g., amphotericin, erythromycin, KCl) and as such, are quickly recognized as culprits in episodes of this form of drug-induced fever. Nevertheless, because clinicians fail to appreciate the capacity of such complications of drug administration to cause extremely high and prolonged febrile reactions, extensive evaluations may be undertaken to diagnose alternative causes of fever in many such patients.

Pyrogenic contaminants. Antibiotics, streptokinase, and certain cancer chemotherapy agents, because they are microbial products, are occasionally contaminated by pyrogens not removed during the production process. Early preparations of vancomycin were plagued by this problem (13), as have been occasional lots of other antibiotics (14). Other drugs, such as amphotericin B appear to be inherently pyrogenic, although one continues to hope that future purification procedures will yield preparations of the drug that are active but non-pyrogenic. Likewise, fever has been the most consistent side effect of interferon therapy, since its earliest clinical trials (15). Dinarello, et al (15) have recently shown that interferon is an intrinsically pyrogenic substance, whose pyrogenic activity does not require mediation by endogenous (leukocyte) pyrogen.

Altered Thermoregulation. Drugs may induce fever by stimulating heat production within the body, limiting heat dissipation or disrupting the function of the thermoregulatory center. Drugs such as dinitrophenol and thyroxine are two of the best examples of drugs that may elevate body temperature by increasing the rate of heat production - such an effect being the consequence of stimulated tissue metabolism (16). Epinephrine, due to its vasoconstrictive activity and atropine, because of its capacity for reducing sweating are two agents having the potential to raise body temperature by decreasing the rate at which heat is dissipated from the body.

Many drugs have been reported to interfere with thermoregulation. Phenothiazines, butyrophene tranquilizers, antihistamines and anti-Parkinsonian drugs with atropine-like activity are but a few such agents (17,18). Both central and periferal effects on the thermoregulatory system have been noted with these drugs (18). The phenothiazines and butyrophenes depress hypothalmic function directly, but also have anticholinergic activity that can inhibit nervous stimuli controlling sweat gland excretion. The disruptive effects of such agents on thermoregulation are compounded when phenathiazines are prescribed with anticholinergic agents (to reduce extrapyramidal side effects). In such cases, the potential for drug-induced hyperthermia is great due to an impaired ability to adjust to elevated environmental temperatures.

Although not generally included in discussions of drug fever, the neuroleptic malignant syndrome is perhaps the most spectacular example of this form of drug-induced fever (19,20). The syndrome is characterized by hyperthermia (core temperatures exceeding 106°F have been observed and have led to confusion of the syndrome with heat stroke), diffuse muscular rigidity, autonomic instability and altered consciousness. It most often occurs as a side effect of haloperidol, but has also been reported in association with other antipsychotic drugs such as the phenothiazines and thioxanthenes. The primary defect responsible for the disorder appears to be inhibition of central dopaminergic systems through dopamine receptor blockade, leading to sustained muscle contraction, excessive heat production and inappropriate cutaneous vasoconstriction. Hyperthermia, dehydration and exhaustion are an inevitable consequence of the condition and, if uncontrolled, may lead to death. Treatment of this disorder is controversial. However, most authorities recommend administration of the periferal muscle relaxant-- dantrolene-- in conjunction with external cooling and other supportive measures. Bromocriptine has also been reported to be effective in some cases of neuroleptic malignant syndrome.

Pyrogen liberation. As a result of the pharmacologic action of a drug, host or parasitic cells may be destroyed in such a way as to release pyrogenic substances into the circulation in quanitities sufficient to elicit a febrile reaction. The classic example of this type of drug-induced fever is the Jarisch- Herxheimer reaction - a febrile reaction accompanied by an exacerbation of cutaneous lesions in syphilitic patents treated with antitreponemal agents such as heavy metals, immune serum or antibiotics (21,22). The reaction is believed to be caused by the release of treponemal substances from dead or dying microbes. The precise identity of these substances is not known. However recent data suggest that they are distinct from classical endotoxin (23). Similar reactions have been described in borreliosis, typanosomiasis and brucellosis (22,24).

Oxamniquine, a new schistosomicidal drug, induces fever as a side-effect in approximately 40% of patients given the drug (25). Although the cause of the fever is not known, the drug does not invoke a febrile response in uninfected adults. Furthermore, a Loeffler-like syndrome with pronounced periferal eosinophilia and scattered pulmonary infiltrates may accompany the reaction, suggesting that the syndrome is due to release of toxins by dead or dying schistosomes.

Cytotoxic agents used to treat malignant neoplasms may induce fever through similar mechanisms. However, in this case, pyrogens are released by dead or dying malignant cells, rather than by pathogenic microorganisms. Such febrile reactions have been reported during high dose cytosine arabinoside therapy of non-Hodgkin's lymphoma (26,27), during bleomycin therapy of lymphomas (28) and during treatment of chronic lymphocytic leukemia with chlorambucil (29).

Genetic determinants. Only in rare instances is there evidence of genetic predisposition to drug fever. Valnes, et al (30), have reported that patients experiencing episodes of aldomet-induced fever are slow metabolizers of the drug (Figure 4). Such depressed metabolism might affect either intestinal mucosal conjugation of the drug or its hepatic transformation, leading to the accumulation of toxic levels of aldomet in the serum or within cells.

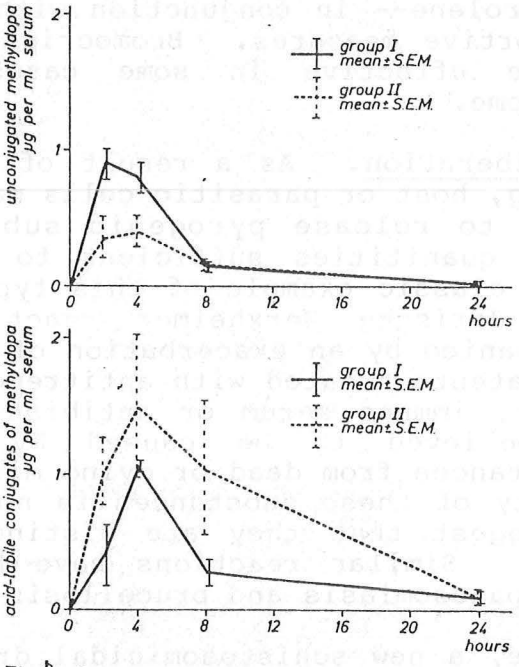

Fig. 4. Serum concentrations of unconjugated (top) and acid-labile conjugated (bottom) α-methyldopa following oral administration of 250 mg α-methyldopa to hypertensive patients with (group I, $n=5$) and without drug fever (group II, $n=5$).

Perhaps the most florid example of drug fever related to a specific genetic defect is that of malignant hyperthermia (31). This is a rare hereditary disorder characterized by rapidly evolving hyperthermia, muscular rigidity and acidosis in patients undergoing general anesthesia. Although various inhalational anesthetic agents have been incriminated in this disorder, halothane (alone or in conjunction with succinylcholine) has been the most common offender. The condition is often prestaged by sudden ventricular ectopic activity, tachypnea, circulatory instability and a sharp rise in body temperature. Metabolic acidosis and rhabdomyolysis are common and frequently severe. Mortality in acute cases varies between 28% and 70%. Although the specific mechanisms responsible for this disorder are still uncertain, a defect in the regulation of intracellular calcium concentration appears to be involved. In susceptible patients, the sarcolemmal reticulum of skeletal muscle appears to be unstable, and releases calcium inappropriately in response to certain anesthetic agents.

Hypersensitivity reactions. Because drug-induced febrile reactions generally occur only after several days to weeks of exposure to the offending agent, are dose independent, recur immediately after a provocative dose of the offending agent, and are occasionally accompanied by eosinophilia, most are thought to be allergic in origin (32-34). During such reactions, antibodies to offending agents appear to develop, followed by the formation of drug-antibody immune complexes (35,36). Such complexes sensitize lymphocytes, which then release a soluble, pyrogen-inducing lymphokine.

THE DALLAS EXPERIENCE

Last year, Fred LeMaistre, M.D. (a former chief resident) and I completed a survey in which we analyzed 51 episodes of drug fever diagnosed at PMH and the DVAMC between 1959 and 1986 and another 97 published case reports (37). Cases of drug fever were identified by reviewing the medical records of patients admitted to the two hospitals. Medical records were sought for all patients having "drug fever" listed as a discharge diagnosis on their hospital record or in records maintained by the infectious diseases services at these two hospitals.

To identify cases of drug fever reported in the literature, a computerized search was performed on BRS medline (1966 - Apr. 1986) using "fever" as the major descriptor with the subheading "classification". The search was limited to "English only" and "human only". Of the 227 citations identified, 64 (2,27-29,34,38-96) contained descriptions of cases of drug fever that both met our case definition (see above) and contained sufficient clinical information for analysis.

Fifty-one episodes of drug fever in 45 Dallas patients and 148 episodes reported in the English literature were identified and analyzed. There was a slight male predominance among cases reviewed (Table 4). Twenty percent of the Dallas cases and 62% of the cases gleaned from the literature were confirmed by rechallenge with the offending agent. Of those rechallenged, only one experienced a complication coinciding with the rechallenge. This Dallas patient extended a prior myocardial infarction, during a febrile reaction to quinidine sulfate. Nine percent of Dallas cases and only 12% of cases reported in the literature gave histories of prior drug allergies. Only three patients in the combined series gave histories of atopic disease. All three had asthma.

Table 4 Clinical features of drug fever.

	Dallas Series (51 episodes*)	Literature (97 episodes)	Total (148 episodes)
	No.	No.	%
Sex (M/F)	27/18	53/44	56/44
No. rechallenged	9	60	47
History of atopic disease	0	3	2
Prior history of drug allergy	4	12	11
Fever pattern (No. reported)	51	41	62
Continuous	0	9	10
Remittent	19	7	28
Intermittent	6	13	21
Hectic	26	12	41
Rigors	26	52	53
Relative bradycardia	5	4	11
Hypotension	6	21	18
Headache	15	9	16
Myalgias	16	11	25
Rash	20	6	18
Pruritis	11	0	7
Leukocytosis ($\geq$ 10,000/mm^3)	17	15	22
Eosinophilia ($\geq$ 300/mm^3)	21	12	22
Associated abnormalities	16	43	40
Gastrointestinal	10	22	22
Genitourinary	5	2	5
Hematologic	1	12	9
Other[1]	0	18	12
Deaths	2	4	4

* 51 episodes in 45 patients

[1] Includes: shock, arrythmias, seizures, altered mental status

Of the fever patterns reported, hectic patterns were the most common. However, these may have been altered in many instances, because patients frequently received antipyretic agents or were subjected to external cooling measures. Except for one report of a "goal post" pattern (Figure 5) (61), none of the patterns observed was sufficiently distinctive to differentiate the febrile response from that observed in patients with sepsis or other febrile disorders. Shaking chills were common in both series, leading physicians to a tentative diagnosis of bacterial sepsis in many instances. As a result, patients were frequently evaluated extensively for bacterial infections and treated empirically with broad-spectrum antibiotic regimens.

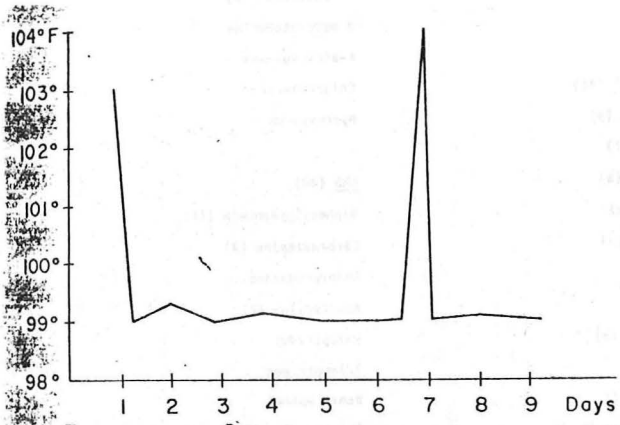

Figure 5. Highest daily temperatures showing "goalpost fever" pattern.

Relative bradycardia (i.e., pulse rate $\leq$ 100/min. during fever) was uncommon, as was hypotension during espisodes of drug fever. In 4 of the 27 instances in which hypotension was observed during the course of drug fever, an antihypertensive drug was the offending agent. Headache and myalgia were observed in 16% and 25% of episodes, respectively. Rashes were seen in 18%; fewer than half were pruritic. Leukocytosis developed in 22% of cases and eosinophilia in another 22%. Eosinophilia was generally mild, with only 3 cases exhibiting absolute eosinophilia counts $\geq$ 1,000/mm^3. Associated organ dysfunction was observed in 40% of episodes and was for the most part, mild. However, 6 patients with drug fever died. In each case, the drug reaction appeared to have been at least a contributing factor in the fatal outcome.

A wide variety of drugs were responsible for the fevers surveyed (Table 5). Alpha methyldopa and quinidine were the two most frequently incriminated. However, as a group, antimicrobial agents were responsible for the largest number of episodes of drug fever. In 7 instances, fever was observed as a complication of drug overdose (five with LSD, and one each with trifluoperazine and benztropine).

Table 5. Agents responsible for episodes of drug fever.[1]

Cardiovascular (38)	Antineoplastic (12)
α methyldopa (16)	Bleomycin (3)
Quinidine (13)	Daunorubicin
Procainamide (6)	Procarbazine
Hydralazine	Cytarabine
Nifedipine	Streptozocin (2)
Oxprenelol	6 mercaptopurine
	L-asparaginase
Antimicrobial (46)	Chlorambucil
Penicillin G (9)	Hydroxyurea
Ampicillin (2)	
Methicillin (6)	CNS (30)
Cloxacillin (2)	Diphenylhydantoin (11)
Cephalothin (7)	Carbamazepine (3)
Cephapirin	Chlorpromazine
Cephamandole	Nomifensine (2)
Tetracycline (2)	Haloperidol
Lincomycin	Triampterene
Sulfonamide (2)	Benztropine*
Sulfa-trimethoprim	Theoridazine (2)
Streptomycin*	Trifluoperazine*
Vancomycin	Amphetamine (2)
Colistin	LSD (5)*
Isoniazid (5)	Anti-inflammatory (3)
PAS	Ibuprofen
Nitrofurantoin (2)	Tolmetin
Mebendazole	Aspirin
Other (19)	
Iodide (6)	
Cimetidine (2)	
Levamisole	
Metoclopramide	
Clofibrate	
Allopurinol	
Folate	
PGE_2 (2)	
Ritodrine	
Interferon (2)	
Propylthiouracil	

[1]Numbers in paretheses indicate number of episodes induced by drugs responsible for multiple episodes.

*Fever observed during drug-overdose

The mean lag time between the initiation of an offending agent and the onset of fever was 21 days (median = 8 days). However, lag times varied considerably from one drug category to another (Table 6). Fever induced by antineoplastic agents had a significantly shorter median lag time than that associated with any other drug category ($p<0.05$ by the Kruskal-Wallis one-way analysis of variance).

Table 6. Relationships between the lag time and offending agent.

Class of	Lag Time*			
Offending Agent	No.	Mean	Median	St. Dev.
Cardiac	36	44.7	10	131.1
Antimicrobial	44	7.8	6	8.4
Antineoplastic†	11	6.0	0.5	12.3
CNS	24	18.5	16	15.4
Anti-inflammatory	2	78.5	78.5	101.1
Other	18	12.1	6	15.3

* Time (in days) between initiation of offending agent and onset of fever

† Significantly shorter lag time than all other agents except for "anti-inflammatory" ($p<0.05$ by the Kruskal-Wallis one-way analysis of variance).

The maximum temperature recorded during episodes of drug fever ranged from 38°C to 43°C. There was an inverse correlation between maximum temperature and age (Figure 6), and no apparent relationship between sex or race and maximum temperature (data not shown). The highest temperatures were observed in association with antineoplastic agents and underlying malignant neoplasms (Figure 7, panels A and C).

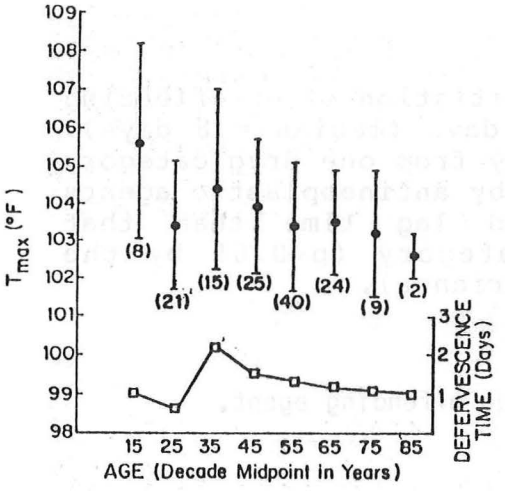

Figure 6. Relationship between age, maximum temperature (.) and defervesence time ( ). Numbers in parentheses indicate numbers of subjects analyzed in each age group.

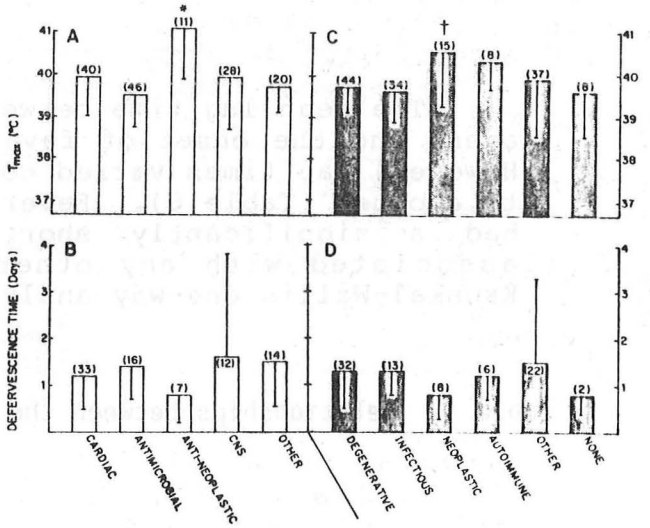

Figure 7. Relationship between drug type (A and B), underlying disease category (C and D), maximum temperature and defervesence time. Numbers in parentheses indicate number of patients available for analysis in each drug category. *Significantly different from every other agent category except for antineoplastic ($p < 0.05$ by the Kruskal-Wallis one-way analysis of variance).

Multivariate general linear model analysis of factors potentially effecting maximum temperatures showed these to be significant associations. However, the relative effects of antineoplastic agents and malignant neoplasms on maximum temperatures could not be determined, because antineoplastic agents were used only in patients with underlying cancers. A comparison of fatal and nonfatal cases showed higher maximum temperatures among fatal cases (Table 7). Fatal cases also had a higher frequency of underlying cancer than nonfatal cases.

The time required for the temperature to return to normal after the incriminated agent was discontinued did not correlate with sex or race (data not shown), age (Figure 6), drug category (Figure 7, panel B), or underlying disease

Table 7. Comparison of fatal and nonfatal cases of drug fever.

Outcome	No.	Age (Years)*	T max (^{o}F)*	Underlying Malignancies†
Fatal	6	46.5±18.3	106.4±2.2	3(50)
Nonfatal	140	47.7+16.8	103.6+1.7	12(8)
P value		N.S.‡	<0.05	<0.05

* Mean ± S.D.

† No. (%)

‡ N.S. = No significant

category (Figure 7, panel D). Patients with brief episodes of fever prior to recognition of the condition and elimination of the offending agent did not differ from those with prolonged episodes of drug fever in terms of either maximum temperatures or defervesence times (data not shown). Similarly, patients with eosinophilia could not be distinguished from those without eosinophilia with respect to either maximum temperature (39.6 ± 0.8 vs 39.9 ± 0.7^{o}C) or defervescence time (1.4 ± 1.0 vs 1.3 ± 1.1 days).

The cost of episodes of drug fever in terms of additional hospital days, diagnostic studies, and treatment could not be determined for cases reported the medical literature due to the lack of relevant information included in such reports. Nevertheless, of the 97 cases analyzed, 39 were admitted to the hospital specifically to evaluate episodes of drug fever. A careful review of the hospital records of Dallas cases revealed a mean prolongation of hospitalization of 8.7 days per episode of drug fever. Each episode was evaluated with a mean of 5 blood cultures, 2.85 radiologic studies, 0.53 courses of antibiotics, 0.86 courses of antipyretics and 0.21 courses of glucocorticoids.

CONCLUSIONS

Much has been written about the clinical characteristics of drug fever, but these writings have been based on random observations in small numbers of cases. The present investigation examines the validity of concepts articulated in this literature through a systematic analysis of a large number of case histories.

It has been written that patients with drug fever generally look relatively well and commonly have normal pulse rates (3,6,33,97). While we were unable to substantiate the former assertion with objective measurements, the case histories reviewed generally depicted patients with few signs or symptoms of serious systemic toxicity. Nevertheless, high fevers with shaking chills were common both among patients seen at the two Dallas hospitals and among those reported in the medical literature. These findings made it difficult to distinguish drug fever cases clincially from patients with bacteremic infections or other febrile disorders. We did not find relative bradycardia to be common in this syndrome.

It has been reported both that a sustained fever pattern is characteristic (6) and that virtually any fever pattern may occur in patients with drug fever (32,97). Our findings support the latter conclusion. We were unable to identify any fever pattern that might be considered typical of this clinical entity. However, it is important to point out that the frequent use of antipyretics and cooling blankets in the cases reviewed could have been responsible for at least some of the variability in fever patterns observed.

In 1964, Cluff and Johnson (32) wrote that the patient developing drug fever "will have a gradually increasing fever beginning on the 7th to 10th day of treatment". Whereas this statement is reasonably consistent with what we observed in patients with drug fever due to antimicrobial agents, we found a considerably shorter lag time for drug fever caused by antineoplastic agents and a substantially longer lag time for fever induced by cardiac agents. Overall, there was great variability in the length of time elapsing between the initiation of different types of agents and onset of fever due to these agents.

It has been stated that "the vast majority of drug fevers are associated with some form of cutaneous manifestation" (7). Our findings do not support this assertion. Skin rashes were reported in only 18% of our cases and less than half of these were urticarial in character. It has also been proposed that eosinophilia is a helpful finding in patients with drug fever (3). We found

eosinophilia in only 22% of the cases reviewed, and in most of these cases, the eosinophilia was mild. Lipsky and Hirschmann have stated that chills, headache, and myalgias are common in patients with drug fever (97). In the present series, chills were seen in 53% of the cases, headache in 16%, and myalgias in 25%.

The incidence of drug fever is known for only a few agents (Table 8). It has been written that "fever as the only manifestation of a drug reaction is infrequent" (1); it has been stated that "fever as the sole or most prominent clinical feature of an adverse drug reaction constitutes approximately 3-5% of these reactions" (33,97), that "fever is extremely common with certain antimicrobials" (4), and that such reactions "occur more frequently than many physicians realize" (2). These pronouncements not withstanding, the actual incidence of this condition is unknown, because neither the appropriate numerator nor denominator data necessary to calculate such rates are available. In addition, it must be assumed that the cases previously reported in the literature, as well as those included in our Dallas series represent only the most severe examples of the disorder and thus underestimate the total number actually occuring.

Table 8. Studies Examining the Incidence of Drug Fever as Induced by Specific Agents

Agent	No. Patients Studied	Incidence (%)	Reference
Ceftriaxone	19	.05	98
Allopurinol	835	0.3	99
Rifampin *	824	.03	100
Timentin	7	.14	101
Aldomet	80	.02	102
Oxamniquine	106	40	25
Steptokinase	107	45	103

* Peculiar flu-like syndrome (fever and myalgias) in 11/27 febrile patients. Syndrome occurred only in patients receiving twice weekly drug regimens.

A recurring theme in most dissertations on drug fever is that any drug has the capacity to induce fever as an adverse reaction. The wide variety of agents incriminated in cases of drug fever considered in the current investigation would seem to corroborate this concept. Nevertheless, if one looks carefully at the list of such agents, it is apparent that some, such as alpha methyldopa, quinidine, and the penicillins are much more likely to be incriminated in this disorder than others, such as the aminoglycoside antibiotics and cardiac glycosides. Thus, whereas the list of drugs having the theoreticial capacity to induce drug fever is long, the list of drugs actually involved in this disorder is considerably shorter. Furthermore, the list is a dynamic one. Important causes of drug fever in the past, such as laxatives, bromides, arsenicals and vancomycin (7,8) are no longer seen in association with this disorder, either because the preparations are no longer used, or because newer preparations of drugs [e.g., vancomycin (13)] are less pyrogenic.

Prior reviews of drug fever have stressed the existence of a number of conditions predisposing patients to the development of drug fever (32,33,97). Systemic lupus erythematosus, severe infections, and atopic allergic diseases have each been so incriminated. It has also been suggested that women and the elderly are at a relatively high risk of developing drug fever (97). We found no such predispositions in our investigation. Although antimicrobials were the most common agents involved in cases of drug fever reviewed, we were not able to determine whether this was due to the inherent pyrogenicity of such agents or to an enhancing effect of the infections being treated on antibiotic pyrogenicity.

More often than not, drug fever is a diagnosis of exclusion made in febrile patients whose fever abates within 48 to 72 hours of discontinuing a suspected pyrogenic agent. Sixty-two percent of the cases reported in the literature and only 18% of the Dallas episodes were confirmed by rechallange with the offending agent. Clinicians might have been reluctant to undertake such rechallenges in many instances, because prior reviews have emphasized that they are neither necessary nor safe (4,8,32,33). Our findings suggest that, while not free from risk, rechallenges with agents responsible for drug fever are associated with a low risk of serious sequelae.

The mechanisms by which drugs induce fever have not been well delineated, nor do the findings of the present investigation provide any new insight into such mechanisms.

The fact that the majority of these reactions occur only after several weeks of exposure to the offending agent, are dose independent, recur immediately after a provocative dose of the offending agent, and are occasionally accompanied by eosinophilia has led many investigators to postulate an allergic basis for such reactions (16,32-34). In spite of the purported role of the eosinophil as an immune modulator of inflammatory reactions (104), we did not find the presence of eosinophilia to have any apparent effect on either maximum temperature observed during episodes of drug fever or defervescence time.

Various forms of therapy have been applied to patients with drug fever. We were unable to evaluate the efficacy of individual treatment regimens such as antipyretics, corticosteroids, and cooling measures in accelerating resolution of the syndrome, because our analysis was neither prospective nor controlled. Nevertheless, the uniformly rapid resolution of fever following discontinuation of the offending agent offers strong support for the widely held conclusion that the only necessary and effective treatment for this disorder is the removal of the drug responsible for the fever.

REFERENCES

1. Bystryn JC: Drug fever. Am J Med Sci 1972, 264:473-474.

2. Jain A, Sanders CV, Nicolle FI: Drug fever during treatment of pulmonary edema. South Med J 1982, 75:1140-1141.

3. Wilkowske CJ, Hermans PE: General principals of antimicrobial therapy. Mayo Clin Proc 1983, 58:6-13.

4. Kirby WM, Turck M: Chemotherapy of infection. In Harrison's Principles of Internal Medicine. 10th Ed. Edited by Petersdorf RG, Adams RD, et al. McGraw-Hill Book Co. New York, 1983, pp. 885.

5. Mann JJ: Fevers of obscure origin. In The Principles and Practice of Medicine. 21st Ed. Edited by AM Harvey, RJ Johns, VA McKusick, AH Owens Jr., and RS Ross. Appleton-Century-Crofts. Norwalk, Conn: 1984, pp. 1001.

6. Hoeprich PD, Boggs DR: Manifestations of infectious diseases. In Infectious Diseases. Edited by Hoeprich PD. Harper & Row, Publishers, Philadelphia, 1983, pp. 87.

7. Dinarello CA, Wolff SM: Fever of unknown origin. In Principles and Practice of Infectious Diseases. 2nd Ed. Edited by Mandell GL, Douglas RG Jr, et al. New York, 1985, pp. 344.

8. Petersdorf RG: Chills and fever. In Harrison's Principles of Internal Medicine. 10th ed. Edited by Petersdorf RG, Adams RD, et al. McGraw-Hill Book Co. New York, 1983, pp. 62.

9. Atkins E: Fever: its history, cause and function. Yale J Biol Med 1982, 55:283-289.

10. Bernheim HA, Block LH, Atkins E: Fever: pathogenesis, pathophysiology and purpose. Ann Intern Med 1979, 91:261-270.

11. Dinarello CA: Production of endogeneous pyrogen. Fed Proc 1979, 38:52-56.

12. Dinarello CA: Interleukin-1. Rev Infect Dis 1984, 6:51-95.

13. Cook FV, Farrar WE Jr: Vancomycin revisted. Ann Intern Med 1978, 88:813-818.

14. Spengler RF, Melvin VB, Lietman PS, Greenough WB III: Methicillin-associated fever. A double blind comparison of methicillin from two manufacturers. Johns Hopkins Med J 1974, 134:28-33.

15. Dinarello CA, Bernheim HA, Duff GW, Le HV, Nagabhushan TL, Hamilton NC, Coceani F: Mechanisms of fever induced by recombinant human interferon. J Clin Invest 1984, 74:906-913.

16. Drug fever. Medical Staff Conference. University of California, San Francisco. West J Med 1978, 129:321-326.

17. Westlake RJ: Hyperpyrexia from drug combinations [letter]. JAMA 1973, 225:1250.

18. Roszell DK, Horita A: The effects of haloperidol and thioridazine on apomorphine - and LSD- induced hyperthermia in the rabbit. J Psychiat Res 1974, 12:117-123.

19. Szabadi E: Neuroleptic malignant syndrome. Br Med J 1984, 288:1399-1400.

20. Knezevic W, Mastaglia FL, LeFroy RB, Fisher A: Neuroleptic malignant syndrome. Med J Aust 1984, 140:28-30.

21. Aronson IK, Soltani K: The enigma of the pathogenesis of the Jarisch-Herxheimer reaction. Br J Vener Dis 1976, 52:313-315.

22. Heyman A, Sheldon WH, Evan LD: Pathogenesis of the Jarisch-Herxheimer reaction: a review of clinical and experimental obserations. Br J Vener Dis 1952, 28:50-60.

23. Young EJ, Weingarten NM, Baughn RE, Duncan WC: Studies on the pathogenesis of the Jarisch-Herxheimer reaction: development of an animal model and evidence against a role for classical endotoxin. J Infect Dis 1982, 146:606-615.

24. Bryceson AD: Clinical pathology of the Jarisch-Herxheimer reaction. J Infect Dis 1976, 133:696-704.

25. Higashi GI, Farid Z: Oxamniquine fever- drug- induced or immune- complex reaction? Br Med J 1979, 2:830.

26. Shipp MA, Takvorian RC, Canellos GP: High-dose cytosine aribinoside. Active agent in treatment of non-Hodgkin's lymphoma. Am J Med 1984, 77:845-850.

27. Carter JJ, McLaughlin ML, Bern MM: Bleomycin-induced fatal hyperpyrexia. Am J Med 1983, 74:523-525.

28. Rosenfelt F, Palmer J, Weinstein I, Rosenbloom B: A fatal hyperpyrexial response to bleomycin following prior therapy: a case report and literature review. Yale J Biol Med 1982, 55:529-531.

29. Sawitsky A, Boklan BF, Benjamin Z: Drug fever produced by chlorambucil. NY State J Med 1971, 71:2434-2436.

30. Valnes K, Hillestad L, Hansen T, Arnolde E: Alpha-methyldopa and drug fever. A study of the metabolism of α-methyldopa in patients and normal subjects. Acta Med Scand 1978, 204:21-25.

31. Gronert GA: Malignant hyperthermia. Anesthesiol 1980, 53:395-423.

32. Cluff LE, Johnson JE III: Drug fever. Prog Allergy 1964, 8:149-194.

33. Kumar KL, Reuler JB: Drug fever. Western Med J 1986, 144:753-755.

34. Neilsen JL, Lund NO: Drug fever due to nomifensine treatment in patients with endogenous depression. Int Pharmacopsychiat 1981, 16:66-68.

35. Atkins E, Francis L: Pathogenesis of fever in delayed hypersensitivity: factors influencing release of pyrogen-inducing lymphokines. Infect Immun 1978, 21:806-812.

36. Chusid MJ, Atkins E: Studies on the mechanism of penicillin- induced fever. J Exp Med 1972, 136:227-240.

37. Mackowiak PA, LeMaistre CF: Drug fever: a critical appraisal of conventional concepts through an analysis of 51 episodes diagnosed in two Dallas hospitals and 92 episodes reported in the English literature. Ann Intern Med (in press).

38. Young EJ, Fainstein V, Musher DM: Drug-induced fever: cases seen in the evaluation of unexplained fever in a general hospital population. Rev Infect Dis 1982, 4:69-77.

39. Foley RF, Parada EA: Drug fever of quinidine. Report of a case and review of the literature. Lahey Clinic Found Bull 1966, 15:49-52.

40. Shapiro MF: Despair, trifluoperazine, exercise and temperature of 108°F. Am J Psychiatr 1967, 124:705-707.

41. Goldstein MR, Kasper R: Hyperpyrexia and coma due to overdose of benztropine. South Med J 1968, 61:984-989.

42. Dole RR: Adverse drug reaction: chills and fever due to procainamide. J Maine Med Assoc 1968, 59:28.

43. Glontz GE, Saslaw S: Methyldopa fever. Arch Intern Med 1968, 122:445-447.

44. Krisko' I, Lewis E, Johnson JE: Severe hyperpyrexia due to tranylcypromine-amphetamine toxicity. Ann Intern Med 1969, 70:559-564.

45. Pierach CA: Drug fever due to procainamide. Minn Med 1969, 52:813-816.

46. Tallgren LG, Servo C: Hyperpyrexia in association with administration of L-alpha methyldopa. A report of two cases. Acta Med Scand 1969, 186:223-226.

47. Ginsberg MD, Hertzman M, Schmidt-Nowara WW: Amphetamine intoxication with coagulopathy, hyperthermia and reversible renal failure. Ann Intern Med 1970, 73:81-85.

48. Friedman SA, Hirsch SE: Extreme hyperthermia after LSD ingestion. JAMA 1971, 217:1549-1550.

49. Jones SE, Moore M, Blank N, Castellino RA: Hypersensitivity to procarbazine (matulane) manifested by fever and pleuropulmonary reaction. Cancer 1972, 29:498-500.

50. Shahawy ME, Flowers NC: Unexplained fever and chills associated with myocardial infarction. Chest 1972, 62:263-265.

51. Rose MS, Bateman DN: Pyrexia with cytosine arabinoside. Br Med J 1972, 4:115.

52. Horn B, Kabins SA: Iodide Fever. Am J Med Sci 1972, 264:467-471.

53. Klein HO, Kaminsky N: Methyldopa fever. Recurrence of symptoms with resumption of therapy. NY State J Med 1973, 73:448-451.

54. Greenblatt DJ, Greenblatt GR: Chlorpromazine and hyperpyrexia. A reminder that this drug affects the mechanisms which regulate body temperature. Clin Pediatr 1973, 8:504-505.

55. Schlutz M, Zinneman HH, Hall WH: Drug fever caused by quinine and quinidine. Minn Med 1973, 56:668-670.

56. Abrams J: Quinidine fever: an unusal manifestation of quinidine allergy. Chest 1973, 64:120-122.

57. Parker WA: Methyldopa hyperpyrexia [letter]. JAMA 1974, 228:1097.

58. Klock JC, Boerner U, Becker CE: Coma, hyperthermia, and bleeding associated with massive LSD overdose: a report of eight cases. Clin Toxicol 1975, 8:191-203.

59. Portnoy J, Torchinsky A, Mendelson J, Kagan J: Febrile reactions after cloxacillin [letter]. Can Med Assoc J 1975, 112:280.

60. Savran SV, Flamm MD Jr: Fever as a toxic reaction to quinidine [letter]. N Engl J Med 1975, 292:427.

61. Murray HW, Mann JJ: "Goalpost fever" [letter]. Ann Intern Med 1975, 83:84-85.

62. Mandell B, Shen HS, Hepburn B: Fever from ibuprofen in a patient with lupus erythematosus [letter]. Ann Intern Med 1976, 85:209-210.

63. Chan W: Less common side effects of methyldopa. Med J Aust 1977, 2:14-15.

64. Yust I, Vardinon N, Fiersteter E, Avramov LA: Levamisole-induced allergy [letter]. Lancet 1977, 1:457.

65. Davis RS, Stoler BS: Febrile reactions to INH [letter]. N Engl J Med 1977, 297:337.

66. Jacobs NF Jr, Thompson SE III: Spiking fever from isoniazid simulating a septic process. JAMA 1977, 238:1759-1760.

67. Greenblatt DJ, Gross PL, Harris J, et al: Fatal hyperthermia following haloperidol therapy of sedative-hypnotic withdrawal. J Clin Psychiat 1978, 39:673-675.

68. Corbell CL, Holdsworth CD: Fever, abdominal pain, and leukopenia during treatment with cimetidine. Br Med J 1978, 1:753-754.

69. Brown JR, Weir AB: Drug fever from tolmetin administration [letter]. JAMA 1978, 239:24.

70. Hankins GD, Leveno KJ: Does ritodrine cause fever? Am J Obstet Gynecol 1978, 132:28-32.

71. Phelen JP, Meguiar RV, Matey D, Newman C: Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E_2. Am J Obstet Gynecol 1978, 132:28-32.

72. Beckner RR, Cananda AT, Ockene IS: Fever due to clofibrate [letter]. N Engl J Med 1979, 301:1345-1346.

73. Dasta JF, Prior JA, Kurzrok S: Isoniazid-induced fever. Chest 1979, 75:196-197.

74. Grenadier E, Keidar S, Marmor A, Palant A: Quinidine and procainamide induced fever in the same patient. Practitioner 1979, 222:685-686.

75. Harris A: Pyrexia and mebendazole [letter]. Br Med J 1979, 2:1365.

76. Jacknowitz AI: Thioridazine-induced hyperpyrexia- a case report. Am J Hosp Pharm 1979, 36:674-678.

77. Sesin GP, Kirschenbaum H: Folic acid hypersensitivity and fever: a case report. Am J Hosp Pharm 1979, 36:1565-1567.

78. Wandless I, Evans JG, Jackson M: Fever associated with metoclopramide-induced dystonia [letter]. Lancet 1980, 1:1255-1256.

79. Mainzer E: A reminder- fever due to methyldopa [letter]. N Engl J Med 1980, 382:174.

80. Safdi MA: Fever secondary to triamterene therapy [letter]. N Engl J Med 1980, 303:701.

81. Stewart CR, Vengrow MI, Riley TL: Double quotidian fever caused by carbamazepine [letter]. N Engl J Med 1980, 382:1262.

82. Ma DDF, Isbister JP: Cytotoxic-induced fulminant hyperpyrexia. Cancer 1980, 45:2249-2251.

83. Hasegawa K, Sakamoto Y, Mitsungagta K, Kashiwagi H: Drug fever due to oxprenolol. Br Med J 1980, 281:27-28.

84. Tiliakos N, Waites TF: Multiform quinidine toxicity. South Med J 1981, 74:1267-1268.

85. Wiener I, Rubin DA, Martinez E, et al: QT prologation and paroxysmal ventricular tachycardia occurring during fever following trimethoprim-sulfamethoxazole administration. Mt Sinai J Med 1981, 48:53-55.

86. Bauman JL, Shulruff S, Hasegawa GR, Roden R, Hartsough N, Bauernfeind RA: Fever caused by hydroxyurea. Arch Intern Med 1981, 141:260-261.

87. Herrmann R, Manegold C, Dieter F: Fever due to 6-mercaptopurine [letter]. Cancer Treat Rep 1982, 66:1785.

88. Kurtz SC, Aber RC: Potassium iodide as a cause of prolonged fever. Arch Intern Med 1982, 142:1543-1544.

89. Shah KA, Greenwald E, Levin J, et al. Streptozocin-induced eosinophilia and fever: a case report [letter]. Cancer Treat Rep 1982, 66:1449-1450.

90. Sheridan WP, King RW, Gerstman M: Fever as an adverse reaction to carbamazepine. Aust NZ J Med 1982, 12:520-522.

91. Smithson WA, Goronert GA, Moss KK: Dantrolene and potentially fatal hyperthermia secondary to L-asparaginase [letter]. Cancer Treat Rep 1983, 67:318-319.

92. Feldbaum JS, Silverstein H: Streptomycin drug fever during treatment of bilateral Meniere's disease. Arch Otolaryngol 1984, 110:538-539.

93. Caraway RD: Febrile reaction following nifedipine therapy. Am Heart J 1984, 108:611.

94. Garnick MB, Ernst T, Martinez F: Acute febrile reaction to streptozocin. N Engl J Med 1984, 311:798.

95. Bedell SE, Kang JL: Leukocytosis and left shift associated with quinidine fever. Am J Med 1984, 77:345-346.

96. Landolfo K, Low DE, Rogers AG: Cimetidine-induced fever. Can Med Assoc J 1984, 130:1580.

97. Lipsky BA, Hirschmann JV: Drug fever. JAMA 1981, 245:851-854.

98. Bradsher RW: Ceftriaxone (RO 13-9904) therapy of serious infection. Antimicrob Agents Chemother 1982, 22:36-42.

99. McInnes GT, Lawson DH, Jick H: Acute adverse reactions attributed to allopurinol in hospitalized patients. Ann Rheum Dis 1981, 40:245-249.

100. Dutt AK, Moers D, Stead WW: Undesirable side effects of isoniazid and rifampin in largely twice-weekly short course chemotherapy for tuberculosis. Am Rev Resp Dis 1983, 128:419-424.

101. Finegold SM, Johnson CC: Lower respiratory tract infection. Am J Med 1985, 79(5B):73-77.

102. Gillespie LF, Dales JA, Crout JR, Sjoerdsma A: Clinical and chemical studies with α-methyldopa in patients with hypertension. Circulation 1962, 25:281-291.

103. Ness PM, Simon TL, Cole C, Walston A: A pilot study of streptokinase therapy in acute myocardial infarction: observations on complications and relation to trial design. Am Heart J 1974, 88:705-712.

104. Bass DA: The functions of eosinophils. Ann Intern Med 1979, 91:120-121.