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Drug Fever

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *In this conference we shall consider the topic of fever due to drugs. Dr. Larry Tierney will lead the discussion.*

DR. TIERNEY:† Since Cluff's report in 1964, fever caused by drugs has not been thoroughly reviewed.[1] The clinical spectrum is broad, the mechanism often poorly understood, and the clinical investigation often stressful and invasive. This review will discuss the physiological background of the various drug fevers as they relate to normal thermogenesis, as well as the range of clinical features observed. In assessing the possible drug origin of fever, one is helped by understanding the generation and regulation of body heat; this topic will be taken up first.

Normal Thermogenesis

In mammals, somatic heat is produced largely by basal metabolic processes and muscle activity. When resting, the liver accounts for much of it; during exercise, the proportion contributed by the muscles rises considerably. Adrenal medullary and thyroid hormones by their influence upon metabolic rate are important in regulation of heat production; this control obtains whether these substances are secreted endogenously or are given as therapeutic agents. Edelman indicates that the mechanism of action of these hormones involves activation of the sodium pump and consequent increase in the rate of mitochondrial oxidative phosphorylation as adenosine triphosphate (ATP) is broken down.[2] This property, that is, the ability to *make* heat, or endothermy, is possessed only by birds and mammals, although other species, the ectotherms, are far more numerous in the animal kingdom. Further, all the dominant land vertebrates, and nearly all animals heavier than 10 kilograms, are endothermic; that is, warm-blooded. From an evolutionary standpoint, endothermy is considered an advantageous trait for survival.[3]

Since heat affects metabolism importantly, it must be closely regulated; for example, enzymes in mammals are optimally active within a fairly narrow temperature range.[4] As no two individual animals are exactly the same, baseline tem-

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perature differs among members of endothermic species; further, normal is best considered as a range, since temperature varies diurnally. If the limits of this diurnal variation are exceeded in either direction, then compensatory mechanisms are called upon to correct the error. As heat is generated by metabolism and by muscle contraction, when the external temperature falls or is low, one shivers, moves around actively, vasoconstricts, and secretes more catecholamines and thyroid-stimulating hormone (TSH). Since heat is dissipated by radiation, conduction and convection, when the ambient temperature rises, then one sweats, vasodilates, hyperventilates and becomes inactive. It is noteworthy that behavior contributes to each of these corrective responses, and is the sole thermoregulatory apparatus of ectothermia. Clothing and buildings with accurate temperature regulation (air cooling and heating) in human society may be considered a very sophisticated behavioral response to the need for thermal regulation.

Fever

The signals to initiate these changes, be they vascular, neural or behavioral, originate in the hypothalamus. A normal hypothalamus is essential for their integration. Fever may be considered a regulated rise in body temperature. Most fevers result from systemic illnesses, principally infectious diseases; the temperature rises because of the same heat-generating physiologic or pathophysiologic events.

In 1878 Billroth recognized the pyrogenic properties of exudates from infected wounds, and early research on bacteria led to the awareness of the presence of endotoxin on the cell walls of Gram-negative organisms. When released, endotoxin, which is heat-stable, causes a brief leukopenia from margination of leukocytes in vessel walls, followed by leukocytosis and delayed fever. In the late 1940's Beeson[5] recovered a small protein from saline extracts of polymorphonuclear leukocytes taken from the ascitic fluid of rabbits with pneumococcal peritonitis. This protein, which is heat-labile, produced immediate fever when injected into rabbits but did *not* lower the leukocyte count. This substance also was pyrogenic for animals made tolerant to endotoxin. Later studies by Wood[6] indeed indicated that endotoxin-induced fever was mediated by this protein, called endogenous pyrogen and released by the neutrophils in the infected animals. It is now known that other cells, monocytes and tissue macrophages throughout the reticuloendothelial system, also elaborate endogenous pyrogen and are quantitatively more important than neutrophils in this function.[7] Lymphocytic lymphokines may stimulate these cells to release pyrogen.

Work by Bodel and Atkins[8] indicates that stimulation of endogenous pyrogen synthesis and release is not caused exclusively by bacterial infection. Other stimuli include antigen-antibody complexes in the blood, immune hyperactivity, and tissue necrosis. It is felt that endogenous pyrogen causes the hypothalamus to initiate thermoregulatory events. Prostaglandins, cyclic adenosine monophosphate (CAMP) and nervous system monoamines also play major roles. In sum, any biological event leading to phagocytosis may lead to production of endogenous pyrogen, and thus to fever. In addition, certain neoplastic conditions, in particular Hodgkin disease and hypernephroma, produce *in vitro* a pyrogen with the same properties as endogenous pyrogen.[9] Endogenous pyrogen, upon reaching the thermosensitive neurons in the anterior hypothalamus, initiates a response identical to exposure to cold. Heat loss is minimized by vasoconstriction, and production increased due to shivering. Body temperature rises, and at a certain elevation of temperature, regulatory reaction ceases. Mechanisms for conservation and dissipation then function as in euthermia, as though a new normal temperature had been reached for that individual animal.

Pathophysiologically, then, a drug might cause a rise in temperature (1) by interference with heat dissipation peripherally, (2) by increasing the rate of metabolism significantly, (3) by evoking either a cellular or humoral immune response, (4) by mimicking endogenous pyrogen structurally and occupying hypothalamic receptor sites and (5) by direct damage to the tissues. This list of mechanisms may be applied to each of the types of drug pyrexia described subsequently.

Drug Reaction

Since this subject falls under the large umbrella of drug reaction, a word of reminder on that problem is in order. Up to 30 percent of patients admitted to hospital will experience a drug reaction, and 2 to 5 percent of patients admitted to hospital have illnesses caused by drugs.[10] Of these latter patients many will have a second reaction

to the same or another drug during their stay. A common drug reaction is hypersensitivity, mediated in large part by antibodies; most drug fevers result from this mechanism. A less common reaction is one of idiosyncrasy, defined as an adverse effect unrelated to the pharmacology of the drug, and not explained by a demonstrable hypersensitivity mechanism. Although many reactions when first reported are thought to be idiosyncratic, as further awareness of pathogenesis develops they tend to be classified as hypersensitive. Both hypersensitivity and idiosyncrasy are unpredictable, reasonably uncommon and appear while pharmacological doses of a drug are given. These types of toxicity account for approximately 25 percent of the total of drug reactions.

Most of the patients with drug reactions have suffered an avoidable and predictable consequence of treatment such as dosage error with resultant end organ damage. Drug fever is usually hypersensitive or idiosyncratic in origin, and consequently is unavoidable and unpredictable (unless complete histories have not been obtained from those obviously sensitive). Even here, however, certain febrile responses to therapy can be prevented by astute clinical observations.

DRUG FEVER

Fever Associated with Administration

What are the ways that drugs cause the temperature to rise in terms of the known pathophysiology of fever? First, there can be febrile states associated with therapy that are not due to the drug itself, but to the manner of its administration. Common examples seen in emergency rooms and in intensive care units are the septicemia and thrombophlebitis associated with plastic intravenous catheters.[11] At least one episode of sepsis monthly is recorded at the San Francisco General Hospital, related to the emergent fashion in which intravenous lines are placed. While not a drug fever as such, this is surely within the definition of a drug reaction. A similar problem is catheter-associated phlebitis, which can be more cryptic; if it involves, for example, a subclavian vein the clinical evidence will consist only of fever and some arm edema. The signs of inflammation are more apparent in peripheral arm veins. Here the source of fever should be no mystery; however, the vein may be concealed by bandages which may serve to both anchor the line and conceal the obvious signs of phlebitis. By dating all such lines and examining them daily, one can prevent costly and inappropriate investigations for fever due to phlebitis. Apart from the foreign body irritation of catheters, phlebitis and fever can also be caused by the caustic nature of some of the drugs; these include cephalothin, vancomycin and diazepam.

Another related cause of fever due to therapy is sterile abscess formation after multiple intramuscular injections. In this disease the clinical findings may not be so impressive as the temperature elevation. Paraldehyde and pentazocine are common offenders. Fever in sterile abscess is due to endogenous pyrogen released from injured and necrotic tissue.

The remaining category of drug fever related to administration is due to endotoxin released by bacteria in intravenous bottles and transfusion packs. The classical clinical picture is that of septicemia, with shaking chills followed by fever. Diagnosis should not be difficult. Although such infection is not common with today's standards for inspection of such materials, epidemics originating from contaminated lots of such innocuous material as 5 percent dextrose and water from certain drug companies have occurred.

Fever Due to Pharmacological Action

Febrile responses that result directly from a drug's anticipated pharmacologic action are rare, but two examples are noteworthy. The first is the Herxheimer reaction, which follows in a few hours the initiation of therapy for spirochetal diseases, such as penicillin for syphilis. Clinically, high fever with chills, myalgias, hypotension and leukocytosis reach maximum intensity about eight hours after drug administration; in secondary lues, the dermatologic lesions may worsen during this period. Pyrexia is due to endotoxin released by the spirochetes. It is not difficult to recognize this phenomenon in a patient specifically under treatment for typical secondary syphilis; however, it may suddenly appear in a patient for whom an antibiotic is administered for an unrelated infection; that is, a patient with undiagnosed or concealed lues. Herxheimer reactions thereby induced in the latent luetic patient given penicillin for another infection can be serious. The effect upon dormant spirochetes in the aorta or brain can lead to encephalopathy or coronary ischemia. A second type of fever results from the direct effect of chemotherapeutic drugs on sensitive

neoplasms, such as Burkitt lymphoma. In this instance, massive cellular necrosis releases endogenous pyrogens which cause fever.

Drug Fever From Altered Thermoregulation

Slight temperature elevations may result from the effect of a drug upon physiological mechanisms which are involved in temperature regulation. This action may not be related to its required therapeutic end-point. Good examples are atropine and congeners (decrease in sweating), catecholamines (vasoconstriction) and thyroid hormones (increased metabolic rate). Endogenous pyrogen is not involved in this type of hyperthermia. These do not cause a clinical problem except with gross overdose and then the clinical features are dramatic. Atropinics like scopolamine can cause a temperature up to 41°C (106°F). However, the patient will be *dry,* since the temperature results from failure of the heat-dissipating ability akin to heat stroke.

As for constrictors, fever is very rarely a clinical problem, and overdoses are most unusual. However, an excess of catecholamine need not be exogenous; pheochromocytoma is a tumor which causes fever and while its hypertensive features usually dominate the picture, it may elevate temperature. When too much thyroid hormone is taken by patients with hypothyroidism, hyperpyrexia, while present, is much less important clinically than other well-known manifestations of thyrotoxicosis. Occasional patients, however, may be receiving thyroxine prescribed by paramedical diet clinics for obesity, and these patients may not know the identity of their medication; diagnosis is likewise more difficult in factitious thyrotoxicosis. Again, in both these cases additional clinical features of hyperthyroidism assist in the diagnosis. In addition to altering physiological control of temperature, drugs can change behavioral responses to external changes of temperature. Sedatives in high doses limit response to environmental stimuli; for example, in hot climates obtunded, particularly elderly, patients may become hyperthermic for this reason.

Drug Fever and Biochemical Defects

A fascinating class are those febrile reactions that are the consequence of a patient's unique biochemical defect which causes metabolic derangements, including fever. The best studied example in this category is glucose-6-phosphate dehydrogenase (G6PD) deficiency. Affected persons upon exposure to an oxidant accumulate oxidized glutathione in their erythrocytes, predisposing them to hemolysis. Fever in this setting is a manifestation of a hemolytic episode with release of endogenous pyrogen from damaged cells.

A truly remarkable drug fever is the malignant hyperthermia of anesthesia.[12] This is a devastating illness with a 70 percent to 80 percent mortality which afflicts primarily young, healthy persons undergoing anesthesia often for trivial operations. Shortly after induction, body temperature rises in these patients as rapidly as four degrees Fahrenheit per hour, to levels approaching 110°F (43°C). Associated findings include tachycardia, lactic acidosis, hyperkalemia, hypocalcemia and a paradoxical muscle rigidity noted after the administration of succinylcholine. The anesthetic employed is usually halothane, but other inhaled gases can behave similarly. At first thought to be an idiosyncratic response, malignant hyperthermia with further scrutiny has disclosed a number of interesting features. It shows a familial pattern with an autosomal dominant inheritance but with variable penetrance, and many patients have positive family histories for adverse events during surgical procedures. Likewise, there is subclinical and in some instances clinical evidence for muscle dysfunction in patients and in their relatives, although they may have no history of anesthetic difficulties. These myopathies take the form of localized weakness or malfunction such as ptosis, hernias, joint hypermobility, and muscle cramps. The serum creatine phosphokinase (CPK) activities in patients and their families are elevated. *In vitro* testing of muscle strips of these subjects shows increased contractility in response to a variety of stimuli, most notably incubation with halothane. This is the key not only to a biochemical abnormality at fault, but also to the high temperature. When normal skeletal muscle is required to increase its rate of metabolism, as in exercise, the increase is mediated by a flux of calcium from the sarcoplasmic reticulum into the myoplasm. Increased concentration of calcium in the myoplasm enhances mitochondrial uncoupling. With increased ATPase activity, uncoupling increases oxygen consumption and converts glycogen to lactate and carbon dioxide; concomitant myofibrillar contractions increase the rate of metabolism.

These processes, both aerobic and anaerobic, stimulate a vast increase in heat production. Such events occur during extreme physical exertion,

which is invariably self-limiting; indeed, body temperature can rise to 40°C (104°F) from voluntary exercise in this fashion. In patients susceptible to malignant hyperthermia, however, the sarcoplasmic reticulum does not accumulate calcium even in the basal state, and that cation is present in greater amounts in the myoplasm. It is thought that halothane notably worsens this mild defect, and produces the metabolic events which normally only occur with exertion. Continued administration of the drug during anesthesia ultimately depletes the muscle of ATP, and muscle membrane integrity and function are lost. Intracellular ions then leak in the direction of the concentration gradient, so that potassium, phosphorus, magnesium and enzymes escape in the circulation. This whole disorder is simply akin to operating one's skeletal muscles at maximum speed indefinitely, and the alarming rise in temperature is totally explained by the heat of metabolism. This is admittedly a rare occurrence but is an excellent example of drug hyperthermia based upon a biochemical anomaly and not upon an allergy.

Indirect Drug Fever

Rarely, drugs can cause fever indirectly from overdose or excessive use. A good example is hemorrhage into the retroperitoneum or thigh, from anticoagulant drugs. As noted, lysis of sequestered red cells can produce a few degrees of fever and must be considered in the differential diagnosis of the anticoagulated patient who is febrile.

Drug Fever Secondary to Hypersensitivity

Drug fever to most clinicians means fever from hypersensitivity. Hypersensitivity drug fever follows the chronology of serum sickness, vis-à-vis the latent period for the patient's reaction to antigen. In serum sickness,[13] urticarial rash, myalgias, fever and arthralgias develop from a few days to two weeks after administration of a foreign protein; immunologically, this corresponds to the period in which relative parity between amounts of antigen and antibody in the circulation allows immune complex formation. A drug or one of its metabolites, either alone or protein-bound, can act as the inciting antigen. The level of complement in circulation falls, and histologically, vasculitis is observed. There may be associated glomerulonephritis, peripheral neuropathy, or indeed, any feature of vasculitis. The parallel of serum sickness and hypersensitivity drug fever is both temporal and histological. Postmortem examinations of patients who have died during a drug fever show evidence of vasculitis akin to serum sickness. Less easily explained is the absence in hypersensitivity drug fever of some other clinical manifestations of serum sickness. Observations of many cases indicate that there may be a spectrum of clinical features, from those of typical serum sickness on one end and fever with no accompanying features on the other. This latter pattern, with fever as the sole reflection of drug *hypersensitivity,* accounts for no more than 3 percent to 4 percent of such reactions. Most of the responsible drugs more often cause serum sickness. These agents include the sulfonomides, penicillins, phenytoin, the barbiturates and methyldopa; theoretically any drug which causes serum sickness can cause hypersensitivity drug fever.

Patients with hypersensitivity drug fever look surprisingly well despite very high temperature, although methyldopa is a striking exception to this dictum.[14] Rechallenge with this drug reproduces symptoms, but this is not advisable, since a death from hepatic necrosis after rechallenge with methyldopa has been reported. The serum sickness model for hypersensitivity drug fever may not hold for methyldopa. Liver function tests are abnormal in a third of patients with this fever, and a positive Coombs test, another side effect of the drug, is *not* observed. Since antibodies directed toward antigens on or in the red cell membrane are required for a positive Coombs test and in methyldopa fever antibodies to drug cannot be shown, some have speculated that this agent may *directly* stimulate pyrogen release from leukocytes. Therefore, the pathophysiology of methyldopa fever may contrast with other hypersensitivity fevers. This might help explain the temperature elevation which is often much greater than with other drugs. Failure to show the presence of antidrug antibodies in no way excludes a serum sickness model explaining the pathogenesis because such antibodies need not be directed against the drug itself. Conversely, the presence of such antibodies does not guarantee pathogenicity. For example, antipenicillin IgG can be shown in sera of patients with no clinical features of drug reaction. Further, other clinical types of hypersensitivity reactions can be antibody-mediated. Although they differ in appearance from serum sickness, they still may stimulate endogenous pyrogen release and cause fever. An

example of this is quinidine-induced thrombocytopenia,[15] in which the immunologic activity is directed specifically at drug antigen coating platelets, but pyrexia may occur. Interestingly, quinidine can also cause a hypersensitivity drug fever with no other manifestations; this emphasizes that even the same drug can elevate the temperature in different ways. A final example of immunologic hyperactivity for which pharmacologic agents are responsible is drug-induced lupus erythematosus. Its pathogenesis remains incompletely understood, but fever, as in natural systemic lupus erythematosus, is one of the clinical features.

A few closing points are of importance. The pattern of fever is not of assistance, except for the goalpost pattern in hypersensitivity drug fever,[16] where drug administered for a febrile condition itself elevates the temperature after several days in the normal range. Usually drug fever shows little diurnal variation, but this is not diagnostically reliable. Other aspects of allergy, if present, are helpful in assigning a drug as causation of the elevated temperature. Past history can be of use if the patient can tell of his previous medications, but this is seldom specific enough; Cluff's paper[1] tells of a mycologist in whom immediate drug fever developed after penicillin administration without ever having received the drug previously. Occupational history showed sensitization to Penicillium in its form as a mold. Often confounding the issue is the circumstance that the drug causing fever is administered for a disease that is in itself adequate explanation for pyrexia. Antibiotics are the best example of this, and more recently, the use of ibuprofen in systemic lupus erythematosus[17] has provided a similar situation. Surreptitious use of a drug poses a problem, and so does noncompliance. We have observed the latter in a patient assumed to be receiving quinidine as an outpatient. Upon its institution after the patient had repeated hospital admissions for chest pain, puzzling fever spikes developed within a day. That these incidents represented inadvertent rechallenge rather than continuation of the outpatient regimen was shown by admission quinidine blood levels of zero. Finally, it is of note that even placebo has been noted to cause fever as an "adverse nondrug reaction."[18]

Drug fever, no matter which mechanism proves responsible, is invariably an easily recognized complication of therapy. It is only required that the clinician always place it in the differential diagnosis of a febrile patient.

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