FEVER: NEW VIEW STRESSES ITS HEALING BENEFITS

By JANE E. BRODY (New York Times)
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THE ancient Greeks, who regarded disease as an imbalance of "humors," believed fever cured the sick by cooking the bad humors and helping the body get rid of them. The notion of fever as beneficial persisted for more than 2,000 years, and countless patients were actually treated with "fever therapy" to aid their recovery from such ailments as syphilis, tuberculosis and even mania.

Then, in the mid-1800's, aspirin compounds that rapidly reduced fevers became commercially available and the medical view of fever changed abruptly. For the next hundred years, physicians and patients focused on bringing down fevers, sometimes with such drastic measures as cold baths and alcohol rubs.

Now, the view of fever is undergoing yet another about-face, thanks to recent research that has in essence documented the benefits suspected by the Greeks. Fever, the studies indicate, evolved at least 300 million years ago in cold-blooded vertebrates as a means of helping the body fight off invading organisms.

The new findings raise serious questions about the wisdom for most people of taking aspirin or acetaminophen for fevers below 104 degrees. Indeed, a number of physicians, including pediatricians, are now suggesting that moderate fevers be allowed to run their course, for they may shorten the illness, potentiate the action of antibiotics and reduce the chances of spreading the infection to others.

These doctors say that fever-reducing drugs should be used with discretion, and some experts even foresee the return of induced fevers to treat selected illnesses. A form of fever therapy is being used experimentally as part of the treatment for some cancers.

Fever, the new studies show, mobilizes the body's immunological defenses against infectious organisms and, in some cases, directly inhibits their growth. Experiments with infected animals, such as fish, lizards, rabbits and dogs, show that those that are allowed to raise their body temperatures are more likely to survive.
In one of the latest studies, people who exercised vigorously were shown to experience some of fever’s effects, which may account for claims of physical fitness buffs that they are less susceptible to ordinary viral and bacterial infections.

"Fever has a high energy cost to the individual," said Dr. Matthew J. Kluger, a physiologist at the University of Michigan Medical School and one of the leading researchers in the revisionist view of fever. "For each 1-degree rise in Centigrade temperature, the body's metabolic rate increases about 10 percent - heart rate, respiration, all the metabolic functions are speeded up."

He added that for this costly response to infection to have been retained throughout the evolution of vertebrates, "it must have a net survival value." In other words, infected animals that developed fever would, on average, have a better chance of living and passing their genes on to the next generation.

The new understanding of fever grows out of basic studies, sponsored primarily by the National Institutes of Health, that have revealed how fevers develop and what changes they induce in the body. Various substances can prompt the development of a fever, among them viruses, bacteria, fungi, toxins, allergens and certain drugs. When the immune system detects such a foreign invader, a type of white blood cell, called a monocyte, is activated and engulfs the intruder.

The activated monocyte, now called a macrophage, releases a hormone, endogenous pyrogen, or EP, which travels through the bloodstream to the brain. There, EP acts on a region of the hypothalamus that regulates body temperature, and raises the body's thermostat, or temperature "set point." The body, which now is not as warm as the brain says it should be, feels chilled and, in effect, turns on its furnace to raise body temperature to the new setting.

Nerve messages originating in the hypothalamus trigger rapid muscle contractions, or shivering, which produce heat. Other nerves constrict outlying blood vessels to reduce heat loss to the environment. Body tissues, such as stored fat, are broken down to produce heat. And the sensation of coldness stimulates behavior, such as putting on warm clothes, piling on covers or drinking hot liquids, that also help to raise body temperature.

In addition to its action on the brain, endogenous pyrogen reduces blood levels of iron and zinc. Studies by Dr. Kluger and others showed that fever increases the amount of iron that bacteria require, and the combination of raised fever and lowered iron inhibits their growth.
He cited a study among Somali nomads who were iron-deficient. When they were given iron supplements to reach a blood level of iron comparable to that usually found in Americans, within a month they experienced a significant increase in malaria, brucellosis and other infections, compared with nomads given placebo capsules.

Dr. Kluger noted that the iron effect may explain the persistence and occasional effectiveness of bloodletting as a treatment, since the loss of blood would reduce iron levels in the body.

Joseph Cannon, a doctoral candidate in Dr. Kluger's laboratory, showed that an hour of pedaling on a stationary bicycle released a pyrogen-like substance into the blood. The blood then caused fever and reduced iron and zinc levels when injected into rats. The exerciser's body temperature also increased and stayed elevated for several hours after the exercise session. Role in Containing Infection

Studies at Yale University School of Medicine have shown that fever, through the action of endogenous pyrogen, helps to contain an infection, preventing its spread throughout the body. The late Dr. Phyllis Bodel found that infectious bacteria injected into lizards will proliferate if the animals are unable to raise their body temperature (by basking under a heat lamp, for example). The lizards die of sepsis, an overwhelming infection carried through the bloodstream. However, if the infected lizards are allowed to warm themselves to fever temperature, defensive white blood cells rush to infection and keep it localized, and the animals then recover.

Her studies helped to explain the results of an earlier experiment by Dr. Kluger. Groups of infected lizards were placed in five chambers, each with a different temperature. Since lizards are coldblooded, the chamber temperature determined how hot their bodies could get. Differences in survival rates were striking: Only 10 percent among those kept at a low normal temperature; 34 percent among those at average normal temperature, and 96 percent of those at fever temperature.

Dr. Bodel, Dr. Harry A. Bernheim, Dr. Elisha Atkins and their colleagues at Yale showed that the net effect of fever is to promote and accelerate the inflammatory response, the body's first-line defense against infection. Immunologically active cells called T cells are stimulated by fever, and they in turn prompt a direct attack on invaders and provoke the development of antibodies to the foreign organisms.
Preliminary studies at the University of Texas Health Science Center in Dallas indicated that antibiotics destroy bacteria more effectively at fever temperatures. At Wayne State University Medical School in Detroit, researchers showed that reducing fever while giving antibiotics to children with infections prevented doctors from recognizing treatment errors, sometimes with serious detriment to the child. The lowered fever masked the fact that the original antibiotic was not working.

Fever also combats viral infections by triggering production of the virus-fighting substance interferon by infected cells. A study of volunteers infected with cold viruses showed that those given aspirin, which reduces fever, release significantly more viruses from their noses and throats than those given a placebo. This viral shedding increases the chances that they will infect other people and also indicates that their own infection is not being controlled. Lysosomes, which are cellular "suicide bodies," are also stimulated by fever and may help to fight viral infections as well as destroy tumor cells, which are more sensitive to heat than normal cells are. Built-in Limit to Fevers

Most fevers are in the range of 100 to 102 degrees Fahrenheit, and there seems to be a built-in limit to how high fevers will go. Rarely does a human fever exceed 106 degrees, a level beyond which serious tissue destruction can occur.

Microorganisms, too, seem to have a built-in propensity to induce or not induce fever, depending on their tolerance of raised temperatures. As Dr. Atkins pointed out, "Organisms that are heatsensitive, like the syphilis treponema, don't induce temperature that would destroy themselves, but the malaria parasite can survive a fever of 105 or 106." Future studies may reveal in which diseases it would be beneficial to induce a fever or raise a mild fever to a higher level.

Fever is not safe for all patients, the experts are quick to point out. The elderly, people with heart disease, newborn infants and others may suffer undue stress from fevers, especially if they are prolonged. Furthermore, very high fevers are likely to cause more harm than benefit, Dr. Kluger said. High fevers can cause delirium, incapacitating chills, convulsions, tissue wasting and undesirable personality effects.

"Clearly, there is some optimum range, with fevers above and below it leading to increased mortality," added Dr. Kluger, who wrote a book on the subject, "Fever: Its Biology, Evolution, and Function," published by Princeton University Press. Though further research is needed to define these limits, he said, science is on the verge of verifying the belief of
Thomas Sydenham, the 17th-century English physician, who said, "Fever is Nature's engine which she brings into the field to remove her enemy."