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# Fever Therapy

Fever as the imminent sign of infectious diseases has been used as a diagnostic indicator since ancient times. The effectiveness of heat as a therapy against disease is believed to be known since 3000 B.C.[1] Parmenides, a Greek physician and philosopher 2500 years ago said, “Give me a chance to create a fever and I will cure any disease.” Fever is one of the body’s best defensive and healing forces, created and sustained for restoring health. Belief in the curative effect of fever was also shared by Celsus, a Roman author of the first systematic treatise on medicine "De Medicina," and Rufus of Ephesus, a Greek physician who lived at the turn of the 1st and 2nd century. Celsus described the hot baths as a tool in the treatment of various diseases.

There has been a historic, cross-cultural recognition of the benefit of fever and heat therapy. The healing effect of heat was first mentioned in the early civilizations of ancient Egypt, where baths in hot desert sand were prescribed for the ill. Doctors of ancient Greece started using this therapeutic approach and named it “overheating” (in Greek: hyperthermia). Other examples are the Roman sulfur hot baths, Finnish saunas, Japanese hot baths, Native American sweat lodges, and the many therapeutic hot springs in Europe, Iceland and in the Americas. Saunas and hot baths do not significantly increase core body temperature enough to have an anti-cancerous effect, but they have been shown to stimulate the immune system. More technologically innovative approaches, however, have developed that increase core temperature or local temperature of tumor tissue to levels that damage or destroy cancer cells.

Fever is a part of the acute phase response to infection and inflammation. We now understand that fever is a complex physiological response that is aimed at facilitating survival of the host. The fever is induced by endogenous inflammatory mediators, such

as prostaglandins and pyrogenic cytokines, that are released by immune cells activated by exogenous pyrogens. Although the pathways (humoral and/or neuronal) responsible for transfer of the pyretic signals from the blood to the brain are still under discussion, it is generally accepted that they act on the level of the anterior hypothalamus to raise the thermoregulatory set-point. Results of studies of the adaptive value of fever demonstrate an association between a rise in body temperature and a decrease in mortality and morbidity during infection. These data, along with data from evolutionary studies, provide strong support for the concept that fever is beneficial during infection in endotherms and ectotherms, vertebrates as well as in invertebrates. There is also evidence showing that fever may be used as a therapeutic tool, especially in cancer therapy.

A fever is the body's highly evolved attempt at destroying invading organisms and to sweat impurities out through the skin. Fever is an effective natural process of curing disease and restoring health. Fever therapy has been shown to be one of the most effective ways of cleansing the internal terrain, re-establishing homeostasis, lifting the “blockade” of the system of basic regulation, and restoring immune mechanisms to normal function.

There is evidence that fever affects cellular immunity by increasing the white cell counts, primarily increasing neutrophils. It has also been shown that fever increases heart rate and may decrease the diastolic blood pressure. Other physiological changes observed are a decrease of serum vitamin-A levels.[2] In 1959, in a review of studies on the effects of heat treatments, Mayo Clinic researchers Dr. Wakim and colleagues, cited findings indicating that the number of white blood cells in the blood increased by an average of 58% during artificially induced fever.

**Bacteria Induced Fever Therapy - William Coley and Coley's Toxins**

The history of bacteria induced fever therapy (fever induction therapy) begins in the mid-19th century with several European physicians. One of the first papers on hyperthermia was published in 1866 by a German surgeon named Carl D.W. Busch. He described the case of a 43-year-old woman with advanced sarcoma on her face. After the tumor was removed, the patient fell ill with erysipelas. The disease induced high temperature which led to tumor regression for over two years. Busch's discovery was fundamental because it was the first reported case showing that high temperature can selectively kill cancerous cells while not affecting normal cells.[3] Along that time others reported that cancer patients who experienced a feverish period after surgery survived significantly longer than patients without fever. In 1882, Fehleisen discovered the erysipelas causative organism as *Streptococcus pyogenes*. He inoculated these live bacteria into 7 cancer patients and achieved complete remission in 3 cases.[3] In the second half of the 19th century, the practice of infectious febrile therapy was quite common - not only in Germany and France, but also in Russia, and it was used to treat a wide range of diseases.

The American surgeon William Coley (1862-1936) also observed that cancer patients often recovered from their cancer if they had suffered a severe post-surgical infection of the wound accompanied by high fever. Coley developed the theory that it was the fever from the infection which had helped patients to recover from their cancer. So he began to treat patients by injecting *Streptococcus pyogenes* directly into inoperable tumors. He found the treatment was most effective when it provoked a fever and a full-blown infection. This led physicians to understand that the increase in body temperature not only mobilized the body's own immune system, thus fighting off the infection, but also destroyed the tumor at the same time.

Later Dr. Coley decided to use a mixture of dead *Streptococcus pyogenes* and dead *Serratia marcescens* bacteria. This "Mixed Bacterial Vaccine" (MBV) was subsequently termed "Coley's Toxin". Mixed Bacterial Vaccines (MBV) contain a combination of heat-

killed bacteria, e.g. gram-positive *Streptococcus pyogenes* and gram-negative *Bacillus prodigiosus*, now called *Serratia marcescens*. In 1943, M.J. Shears, researcher at the National Cancer Institute, discovered that the biologically active substance in Coley's Mixed Bacterial Vaccine is lipopolysaccharide that occurs in the cell walls of gram-negative bacteria.

In 1893, the first patient to receive Coley's Toxin was John Ficken, a sixteen-year-old boy with a massive abdominal tumor. Every few days, Coley injected this bacterium directly into the tumor mass and produced the symptoms of an infectious disease, but did not produce the disease itself. With each injection, there was a dramatic rise in body temperature and chills. The tumor gradually diminished in size, and after four months of intensive treatment, the tumor was a fifth its original size. Later that year, the remains of the growth were barely perceptible.[4] The boy received no further anticancer treatment and remained in good health until he died of a heart attack 26 years later.

Over the next 40 years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. By the end of his career, Coley had written over 150 papers on this subject.[5, 6, 7] Coley mainly used his toxins on patients with inoperable bone and soft-tissue sarcomas, observing that this treatment was less effective on other types of cancer such as melanomas and carcinomas. In 1899, Parke Davis and Company began preparing Coley's Toxins, so they would be available for all physicians. They were widely used for the next 30 years.

In the first half of the 20th century, different formulas of Coley's Toxins were manufactured by several pharmaceutical companies. Standardized commercial bacterial extracts similar to Coley's Toxins appeared on the market in the 1950s and 60s (MBV-mixed bacterial vaccine, Bayer; Vaccineurin, Suedpharma; Picibanil, OK-432, Chugai). These formulations were used to treat patients with a variety of types of cancer until the early 1950s, when other forms of cancer treatment became more widely used, such as radiotherapy. Despite his reported positive results, Coley's Toxins

came under a great deal of criticism because many doctors did not *believe* it possible. Medicine has always been, and still is, ruled by belief.

Additional controversies surrounding Coley's work reflect the field of oncology struggling to stabilize its understanding of how to treat cancer. For example, James Ewing, perhaps the most famous cancer pathologist in the country, was a leading opponent of Coley's work. This was a problem for Coley because Ewing was Medical Director of Memorial Hospital, and for many years was Coley's boss. Their memos to one another reflect constant interpersonal animosity. Ewing himself had become a fanatical supporter of radiation therapy for the treatment of all bone tumors and repudiated any other theories for the treatment of cancer. Ewing therefore refused Coley permission to use his toxins at Memorial Hospital. This was ironic, because Coley had more experience than any other surgeon in the country in treating the small round blue cell sarcoma that still carries Ewing's name.

Skepticism and criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxin to gradually disappear from use in the U.S. By 1952, the Parke Davis Company no longer produced Coley's Toxin, and, in 1962 the FDA refused to acknowledge Coley's Toxin as a proven drug.[8] Thus, in 1962, it became illegal to use Coley's Toxin for the treatment of cancer in the United States. In Europe, Australia and Asia, however, bacteria-induced hyperthermia continued in certain medical circles, and has become an advanced immunotherapy. In retrospect, William Coley's intuitions were correct. Using fever induction therapy to stimulate the immune system is effective in treating cancer. Coley was a model of the clinician-scientist, treating patients and using his practice to initiate research and build theories. But he was a man before his time, and he met with severe criticism.

During the second half of the 20th century, characterized by the heavy use of antibiotics, fever was regarded by mainstream medicine as an unnecessary, weakening state which should be suppressed or prevented. The situation today has not changed much. The immune system is constantly repressed with anti-microbials and even mild

fever is suppressed with anti-febriles. Since fever is metabolically expensive, it must provide substantial advantage to the host. Surprisingly little is known about immunological effects mediated by fever, a lack of understanding that might be attributable in part to the common ignorance in clinical practice with respect to the benefits fever might provide. Post-operative infections can prolong survival: patients developing empyema after lung cancer surgery have an improved 5-year survival. In this light, it seems unfortunate that fever is usually suppressed in hospital routine.[9]

## The Modern Development of Fever Induction and Immune Response

Fever induction therapy today involves the injection of specific bacterial lysates, which induce the release of cytokines, and bring about a fever reaction. The immunological response of cytokine release with underlying fever has been extensively researched over the last several decades. Direct endogenous pyrogens, or proteins that produce fever, are associated with IL-1alpha, IL-1beta, TNF-alpha, TNF-beta (lymphotoxin-alpha), IL-6, macrophage inflammatory protein 1, and IFN-alpha.[10, 11, 12] Indirect fever inducers are IL-2 and IFN-gamma.[13] Most fever response usually only reaches a maximum of around 39°C (102°F), which is not sufficient to induce enough thermal damage within cancerous tissue. However, the immunological effect of this treatment can greatly improve the general condition of the patient through stimulating immunity, resulting in a positive response.[14, 15] Since there is much evidence that fever alone can have beneficial effects, experiments using pyrogenic cytokines for treatment of cancer (e.g. interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), ciliary neurotropic factor (CNTF), interferon-(IFN)-alpha) should discuss cytokine and fever effects separately.

Tumor cells are more vulnerable to heat than normal cells and undergo necrosis to a larger extent.[16, 17] Immunogenic Heat Shock Protein-peptide complexes are displayed to a larger extent on cancer cells after heat treatment, at least in some cancers.[18, 19] This is an interesting feature, since these complexes can activate natural killer (NK) cells[20], offering a second defense line independent of major histocompatibility complex-restricted immunogenicity provided by CD4+/CD8+ T cells. Today, cancer

immunotherapy is roughly divided into cancer vaccine therapy, dendritic cell therapy, and activated lymphocyte therapy. Activated lymphocyte therapy includes T-lymphocyte (T-cell) therapy, natural killer-cell therapy, natural killer T-cell therapy, and gamma-delta T-cell therapy. This has prompted interest in the development of innovative cancer therapies that are based on the manipulation of NK and NKT cells. Fever is a natural immunotherapy mechanism. It is also thought that fever can generate a missing costimulatory signal via dendrite cells needed by resting tumor-specific T cells for full activation, followed by partial or complete “spontaneous” regression in some established tumors, to eradication of dormant cancer cells in a young tumor (prevention) or to eradication of residual cancer cells after surgery (improved survival after postoperative infection).[21, 22, 23]

Research studies explain the anti-tumor effect of Coley’s Mixed Bacterial Vaccine through induction of interferon, augmentation of natural killer cell activity, stimulation of lymphoid tissues, activation of macrophages, induction of serum factor that causes necrosis of tumors, as well as stimulation of interleukin 2.

Fever therapy not only has a significant effect on the immune system, but on other defense mechanisms as well: especially the extracellular matrix or “regulatory ground system,” which is the system of basic bioregulation. Clinical research suggests that the restoration of basic regulatory mechanisms appears to be an important precondition for specific immunotherapy to reach its optimal effect.

Fever therapy has been shown to be one of the most effective ways of cleansing the internal terrain, re-establishing homeostasis, and restoring immune mechanisms to normal function. Today we can induce and control fever much better than 100 years ago. (See Hyperthermia.) Fever therapy for chronic infections and certain cancers, and the importance of fever should be re-opened for further research.

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