

Fever, Cancer Incidence and Spontaneous Remissions

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Key Words

Fever · Cancer incidence · Spontaneous remissions · Immunology · Epidemiology

Abstract

Objective: Accumulating evidence exists for (1) an inverse correlation between the incidence of infectious diseases and cancer risk and (2) an inverse correlation between febrile infections and remissions of malignancies. This review is part of an effort of the Office of Alternative Medicine at the National Institutes of Health to examine this evidence. **Methods:** A review of the literature to a key word search was undertaken, using the following key words: fever, infectious diseases, neoplasm, cancer incidence and spontaneous remission. **Results:** The data reviewed in this article support earlier observations on the topic, i.e. that the occurrence of fever in childhood or adulthood may protect against the later onset of malignant disease and that spontaneous remissions are often preceded by feverish infections. **Conclusion:** Pyrogenic substances and the more recent use of whole-body hyperthermia to mimic the physiologic response to fever have successfully been administered in palliative and curative treatment protocols for metastatic cancer. Further research in this area is warranted.

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Introduction

Cancer patients often suffer from immunological deficiencies due to tumor load and aggressive therapies. The development of growth-stimulating factors such as colony-stimulating factors or erythropoietin has successfully overcome some of the obstacles associated with toxic chemo- and radiation therapies in cancer treatment. However, growth factors often achieve only palliative and short-term effects on long-term immunological defects in clinical and outpatient settings. Exposure to endotoxins has been shown to act as a powerful enhancer of immunity in immunocompromised cancer patients and other patient groups by reversing virally mediated immunosuppression [1, 2]. However, cytotoxic therapies often exert long-lasting immunologic depression with the subsequent risk of secondary malignancies [3–16].

There is a need for new treatment approaches in cancer therapy [17–19], and some authors recommend a new paradigm in cancer treatment [20–22]. Although our understanding of the genetic mechanisms mediating carcinogenesis and tumor growth is improving, gene therapy is successful only in a few cancer entities and the cancer problem remains unresolved.

Dr. William B. Coley (active career 1890–1936), the leading bone surgeon at Memorial Sloan-Kettering Cancer Center of his time, is now often called the father of

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modern immunotherapy. Early in his career, Coley witnessed the spontaneous remission of a large lymphosarcoma of the head and neck in a patient following a massive streptococcal-induced erysipelas infection. He subsequently deliberately exposed his cancer patients to heat-inactivated cultures of *Streptococcus pyogenes* (exotoxin-containing gram-positive organisms) and *Serratia marcescens* (endotoxin-containing gram-negative organisms) [23–31]. With this treatment approach and the staging methods of his time, Coley achieved a cure rate of approximately 10%, which at that time was unsurpassed in the treatment of advanced cancer [reviewed in ref. 32]. In the following decades, researchers isolated a lipopolysaccharide from endotoxins as one of the active principles of Coley's toxin. In an attempt to reproduce Coley's results, researchers may have underestimated the contribution of the exotoxins, which are now known in cancer immunology as superantigens [33, 34]. Yet, it was the combination of a gram-negative and a gram-positive bacterial mixture that led Coley to his results. Additionally, the presensitization of the host with bacillus Calmette-Guérin (BCG), given the high prevalence of BCG infection in the population at that time, may have played an important role in the successful treatment outcome. It was a BCG-primed mouse in which tumor necrosis factor (TNF) was discovered in 1975 and the concept of presensitization is well known in immunotherapy. BCG has been used as an adjuvant treatment in different cancer models [35–41].

Incidence of Malignancies and Missing History of Fever

Clinical oncologists repeatedly report that cancer patients stress in their history that they were never ill before the onset of cancer. As a result of this observation, a number of epidemiological studies have been conducted. In 1894, Laurence [42] acknowledged the fact that cancer patients have a '... remarkable disease-free history ...'. In 1910, Schmidt [43] confirmed these findings in observing 'afebrile (missing fever) diathesis (constitution)' in the case histories of 241 cancer patients. Later, in 1934 and 1935, Engel [44, 45] observed a similar finding when comparing 300 cancer patients with 300 patients not suffering from cancer. Individuals who had never experienced a febrile infectious disease were 2.5–46.2 times more likely to have developed cancer than those who had had febrile infections. In 1936, Sinek [46] reported similar results for 232 cancer patients and 2,444 controls.

More recent studies confirm the earlier work. Witzel [47] analyzed the history of 150 cancer patients and 150 patients without cancer. In this study, cancer patients had significantly fewer visits to physicians, secondary illnesses and inpatient hospital referrals. Also, in the 5 years preceding the diagnosis, 2 cancer patients had developed fever compared with 20 controls. In a study of 300 women with ovarian cancer, Newhouse et al. [48] correlated sociological factors and found fewer marriages and lower incidences of mumps, measles or rubella in the cancer group compared to an age-matched control group. Remy et al. [49] found an increased risk for cancer among patients who had no [odds ratio (OR) = 2.6] history of former infectious organ diseases, no history of common colds (OR = 5.7) and no history of fever (OR = 15.1). Grufferman et al. [50] studied environmental factors in the etiology of rhabdomyosarcoma in childhood. It is the only paper that found no correlation between fewer immunizations, a higher rate of preventable infections and cancer risk. Rønne [51] was able to associate a missing history of measles in childhood with increased cancer risk for a variety of tumors in a historical prospective study. Out of 353 individuals with a negative history of measles, 21 developed cancer versus 1 case from the 230 controls who had a positive history of measles ($p \leq 0.001$) [51].

Van Steensel-Moll et al. [52] reported a lower frequency of infections in the first year of life for children with leukemia. In this register-based case-control study, common colds, periods of fever and primary childhood infections were associated with reduced relative risks (RR) of 0.8 [95% confidence interval (CI) 0.2–1.3], 0.9 (95% CI 0.3–1.5) and 0.8 (95% CI 0.4–0.7), respectively. The authors argue that stimulation of the immune system in early life may play a protective role against the development of leukemia. Chilvers et al. [53] performed a retrospective study evaluating the impact of the absence of common colds or allergies, but not the absence of fever or infectious diseases, on cancer risk. In this study assessing the absence of a history of common colds or allergies, no association with increased cancer risk was established. Remy et al. [49], Abel [54, 55], Abel et al. [56] and Schlehofer et al. [57] reported different results. Abel et al. [56], in a case-control study with 255 cancer patients compared with 230 controls, showed that patients who had the highest risk for cancer were those with a low 'infection index'. In a population-based case-control study, Schlehofer et al. [57] compared the medical risk factors of 226 patients with primary brain tumors to those of 418 controls. They reported a decreased RR for the incidence of brain tumors among individuals who had had allergic diseases (RR 0.7,

95% CI 0.5–1.0), diabetes (RR 0.7, 95% CI 0.3–1.8) and infections and colds (RR 0.3, 95% CI 0.1–0.8). Melanoma patients had fewer ($p \leq 0.05$) atopic symptoms than did control subjects. Grossarth-Maticek et al. [58] performed a 10-year prospective cohort study of 1,353 persons. They concluded that ‘episodes of high fever during the entire life span in the case of an acute illness as a typical reaction are inversely related to later cancer incidence when the subjective reporting of fever is accepted as valid evidence’. Kölmel and Compagnone [59] investigated the role of fever and atopy in melanoma patients. Among melanoma patients, there were fewer feverish infections. Finally, Kölmel et al. [60] demonstrated an inverse relation between the number of febrile infections and the incidence of malignant melanoma in 271 controls versus 139 melanoma patients.

The correlation between a missing history of fever and cancer risk could not be confirmed for acute adult leukemia in a recent study [61] with 624 patients with acute myeloid leukemia and 124 patients with acute lymphoblastic leukemia who were matched with 637 healthy population controls. The study did not support the notion of a protective effect of antigenic stimulation on the risk for acute leukemia in adults.

When discussing the incidence of malignancies and missing history of fever, the same question can be asked in relation to immunosuppressive drugs. There is considerable evidence that a higher cancer rate accompanies transplantation surgery after the introduction of immunosuppressive methods [15]. Data showing increased incidence of neoplasms following therapeutic immunosuppression exist for lung carcinoma [62], lymphoma [63–65], bladder tumors [66] and mixed tumors [9, 67–72]. Although some patients who develop *de novo* malignancies have readily treatable *in situ* carcinomas of the cervix, low-grade skin tumors or *in situ* carcinomas of the vulva and perineum, these data deserve increased attention. The controversy as to whether immunosuppressive or chronic immunostimulatory events mediate increased carcinogenesis persists, while possible mechanisms remain uncertain.

Fever and the Immune Response

Fever as the imminent sign of infectious diseases has been used as a diagnostic indicator since ancient times [73]. It is one of the oldest nonspecific responses to infection, both in vertebrates and invertebrates [74]. A rise in temperature during fever establishes a cascade of host

defense mechanisms that increases host survival and induces T cell proliferation and differentiation, secretion of interferons (IFNs), antibodies and neutrophil migration [75, 76]. Fever as a part of the acute-phase reaction and the role of cytokines in thermoregulation have been reviewed recently by Dinarello [77, 78].

The interest in fever as a therapeutic tool dates back to Parmenides (ca 540–480 BC), who stated: ‘Give me the power to induce fever and I will cure all diseases’. In the 17th century, the English physician Sydenham (1624–1689) described the reaction of the organism to pyrogenic substances as follows: ‘... fever is a mighty engine, which nature brings into the world for the conquest of her enemies’. Ever since Burnet [79, 80] postulated the theory of immunological surveillance and the limitations of aggressive cancer treatments became obvious, research has focused on the possible role of the immune system in cancer incidence and prognosis. As has been shown and will be discussed further, the role of fever as an innate and very old phylogenetic mechanism deserves the best of our scientific attention as a tool in the ongoing search for the treatment of cancer.

Spontaneous Remissions and Feverish Infections

The extensive literature on spontaneous remissions in cancer following infections with or without fever has been reviewed by O’Regan and Hirshberg [81]. The older literature consists mainly of reports by Dr. William B. Coley, which were meticulously documented in 18 monographs by his daughter Helen Coley Nauts [82–101].

Analysis of the literature reveals that feverish infection is associated with remission in $\geq 22\%$ of leukemia cases, followed by $\geq 15\%$ of cancers of the bone and connective tissue, $\geq 11\%$ of melanoma cases and $\geq 7\%$ of lymphoma cases [81]. Spontaneous tumor remissions during or following feverish infections had been reported previously at the beginning of the 19th century [102, 103]. There are several older reports of spontaneous remissions [104–106] as well as recent studies by Everson [107, 108], Everson and Cole [109, 110], Stephenson et al. [111], Cole [112–114] and Nauts [94]. Remissions of leukemia following systemic infections have been noted throughout this century [115–117]. Stephenson et al. [111] reported that an infection or persistent fever preceded 224 cases of spontaneous remissions. Additionally, febrile infections have been shown to increase the survival expectancy of cancer patients [118–122]. Nowacki and Szymendera

Table 1. References reporting infection and/or fever in association with spontaneous remission of neoplastic diseases

Tumor types	References
Bone tumors	112, 144–148
Burkitt's lymphoma	151
Brain tumors	122, 149–150
Colorectal cancer	123–124
Gastric cancer	152–153
Gynecological	154–155
Head and neck cancer	156–157
Hepatocellular cancer	158–161
Leukemia: AML, ALL, CML, CLL	115–117, 121, 125, 162–182
Lung cancer	119–120, 182–184
Lymphoma and non-Hodgkin lymphoma	151, 185–196
Melanoma	126, 197–202
Multiple myeloma	203
Prostate cancer	204
Renal cell cancer	205–207
Retinoblastoma	208–211
Sarcoma	95, 211–217

AML = Acute myeloid leukemia; ALL = acute lymphatic leukemia; CML = chronic myeloid leukemia; CLL = chronic lymphatic leukemia.

[123] reported a highly unfavorable prognostic significance for postoperative fever and/or septic complications in colorectal cancer patients. Fucini et al. [124] disagreed with this statement based on their retrospective analysis showing no significant prognostic influence of postoperative fever and/or septic complications in this patient group.

Treon and Broitman [125] described posttransfusional hepatitis as a common complication in patients with acute myelogenous leukemia and one which paradoxically prolonged survival. They identified the impaired hepatic endotoxin (lipopolysaccharide) clearance in patients with acute viral hepatitis as the reason for endotoxemia and elevated TNF- α release, a mechanism described as endothelial translocation. They also observed that virally induced IFN- γ secretion acts as an antiproliferative agent in synergy with TNF- α to induce differentiation. Finally, in a recent monograph on spontaneous remissions of malignant melanoma, Maurer and Kölmel [126] listed 21 cases from the world literature in which febrile infections have been associated with spontaneous regression of metastatic melanoma. These authors concluded that 'the connection of febrile infection and tumor regression is the most frequent association found in the literature' [126]. Table 1

provides a summary of the literature on spontaneous remission of neoplastic diseases associated with infection and/or fever.

Interaction between the Neuroendocrine and Immune Systems

Increasing evidence suggests a complex bidirectional interaction between the neuroendocrine and immune systems. Of course, a thorough review of this subject [for a review, see ref. 127, 128] is well beyond the scope of this brief overview of fever and cancer. Some essential linkages between neuroendocrine and immunologic pathways are shown in figure 1. During acute febrile illness, which is characterized by fever, inactivity, fatigue, anorexia and catabolism, neuroendocrine and metabolic changes initiate an acute-phase response mediated by cytokines. Acute-phase proteins are produced by the liver and bone marrow function and metabolic activity of leukocytes are increased while specific immune reactivity is suppressed. It has further been shown that fever-inducing signals of the immune system to the brain also stimulate the hypothalamic-pituitary-adrenal axis [129]. The vagus nerves promote these brain effects on systemic cytokines, while circumventricular vascular organs themselves produce cytokines. The primary endogenous pyrogens in this system are proinflammatory cytokines like interleukin (IL)-1, IL-6 and TNF- α , which modulate the activities of catecholamines and serotonin during the acute-phase response [130, 131].

Some Immunological Aspects

Cytokine research has elucidated some of the immunological responses underlying fever. Direct primary endogenous pyrogens include IL-1 α , IL-1 β , TNF- α , TNF- β (lymphotoxin), IL-6, macrophage inflammatory protein 1 and IFN- α [132]. Indirect inducers include IL-2 and IFN- γ [77]. Exogenous pyrogens are considered to be the lipopolysaccharides of the cell wall of gram-negative bacteria such as *S. marcescens* and the exotoxins of gram-positive bacteria such as streptococci and staphylococci, which are also called bacterial superantigens. Fever-induced temperature changes have been shown to augment immunologic defense mechanisms in vivo and in vitro [132–136]. Increased temperatures stimulate the proliferation but not cytotoxicity of cytotoxic T lymphocytes, which can perform effector functions at all physiological tempera-

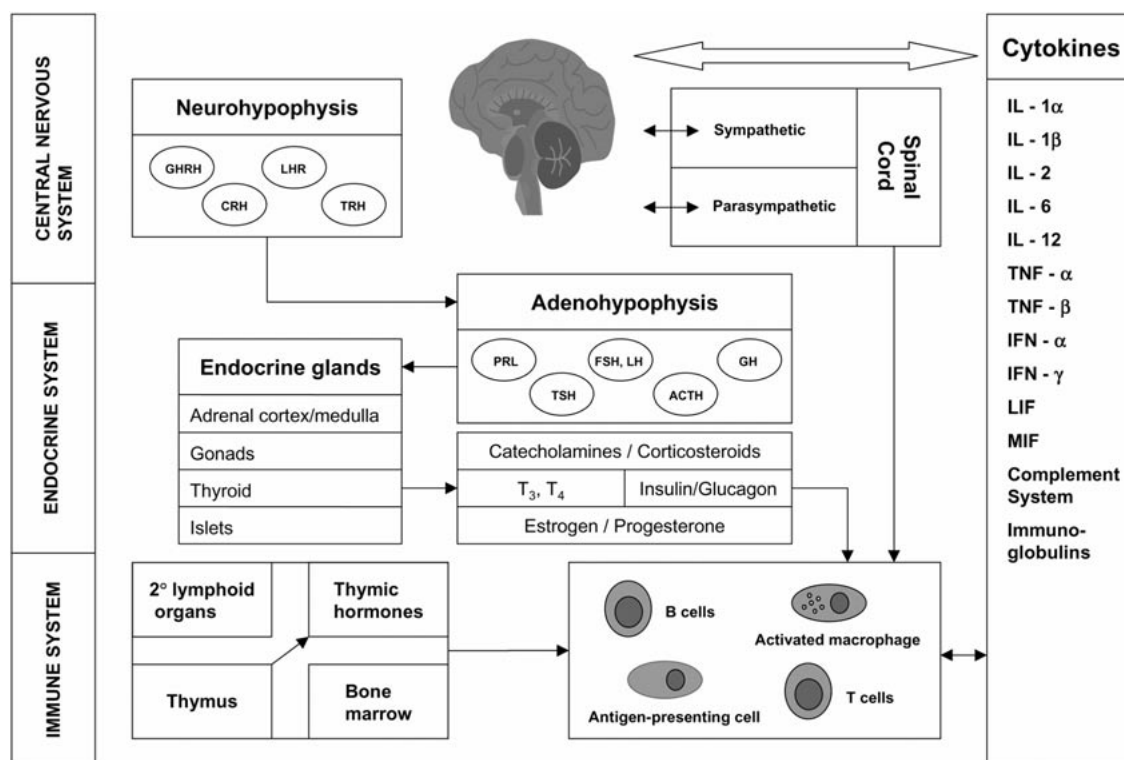


Fig. 1. The complex bidirectional communication pathway between the central nervous system (CNS), the endocrine system and the immune system. The immune system can be influenced by complex innervating loops from the central nervous system and/or the endocrine system. Conversely, lymphoid cells and cytokines modulate higher functions in the central nervous system. ACTH = Adrenocorticotropic-releasing hormone; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone-releasing hormone; LH = luteinizing hormone; LHR = luteinizing hormone-releasing hormone; LIF = leukemia inhibitor factor; MIF = macrophage inflammatory protein 1; PRL = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

tures in the body [132, 137–139]. An example of this phenomenon is observed in virology. At higher than physiologic temperatures, binding of bivalent antibody can neutralize picornaviruses by irreversibly neutralizing the virus through disruption of the virion, which leads to ejection of RNA. Fever enhances this process *in vivo*, confirming the popular belief in the virtues of fever [140].

Not all researchers report enhanced immunity, however, since incubating temperatures of 39°C have been shown to suppress natural killer cell activity *in vitro* in the presence of IL-1 or IFN- α [139].

There are major neuroendocrine and metabolic alterations during febrile illness, the end result of which is a rapidly amplified innate immune defense, coupled with numerous other measures that protect the host.

Glucocorticoids have both stimulatory and inhibitory roles in febrile illness. For example, the production of

acute-phase proteins and natural antibodies is augmented by glucocorticoids and catecholamines [reviewed in ref. 141]. On the other hand, glucocorticoids inhibit various components of the acute-phase response, particularly the increase in body temperature induced by endotoxins. Endogenous glucocorticoids function as part of an inhibitory feedback system that modulates fever by decreasing plasma IL-6, colony-stimulating factor and prostaglandin (prostaglandin E₂ and prostaglandin F_{2 α}) concentrations [142]. Extensive tissue damage due to trauma is capable of inducing a febrile reaction in the absence of infectious agents [143]. This may be true also for advanced cancer. Therefore, it is tempting to speculate that at least some of the recorded cases of spontaneous remission after a febrile reaction were actually directed against cancer and not against a concomitant infectious agent.

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