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REVIEW

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Fever and cancer in perspective

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Abstract *Context:* A relationship between feverish infection and concurrent remission from cancer has been known about for a very long time. However, a systematic investigation of the phenomenon has not yet been made. *Objective:* To bring together the isolated observations about the coincidence of spontaneous remissions with feverish infections and William Coley's seminal work, as a basis for devising an immunological hypothesis about the putative anti-cancer effect of fever. *Conclusion:* Fever induction under medical guidance may be considered as part of a therapy regimen for cancers of mesodermal origin.

Introduction

These days fever is typically regarded as an unpleasant, unnecessary, weakening state, which should, by default, be prevented. Its "guilt by association" remains firmly entrenched in most areas of current medicine. This opposition to fever was not always the case. Parmenides (about 540–480 B.C.) said: "give me the power to induce fever, and I cure all diseases." For many centuries, with the exception of the most recent, fever has been regarded as a mighty and powerful mechanism for fighting diseases of all kind, including cancer. Deidier, in 1725, pointed out that tumors of syphilitic patients were cured more often than others and that prostitutes infected with syphilis had a lower frequency of cancer than the average population [12]. In the eighteenth and nineteenth century, it was well known – but is almost forgotten today – that cancer patients who get a bacterial infection sometimes show a concurrent remission.

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The Busch-Coley treatment

In the issue of 13 March 1868, of the *Berliner Klinische Wochenschrift*, Prof. Busch reported, perhaps for the first time, an experiment with a human patient in which an attempt was made to treat cancer by fever induction [7]. Busch had previously observed a resorption of tumor mass in some patients with sarcoma of the face or neck after they got an erysipela: a severe skin infection caused by *Streptococcus pyogenes*, which is accompanied by a heavy and acute inflammatory reaction. A 19-year-old female patient with a child-head-sized sarcoma of the neck gave him the opportunity to test the effect of a guided erysipela infection. It was not possible to culture bacteria in those days, so he took the cotton-wool bandage of a second patient with acute erysipela infection and applied it onto a small burn injury on the neck of the sarcoma patient. She developed the typical erysipela rose, her temperature increased to 40 °C over several days, and the huge tumor shrank to the size of a small apple within 2 weeks. Unfortunately, the patient developed severe circulatory problems and all efforts had to be taken to fight the infection and raise her strength. After the infection was cured, the tumor grew again, and the patient left the clinic, with an unknown fate.

In 1882, Fehleisen identified *Streptococcus erysipelatos* (now called *Streptococcus pyogenes*) as the pathogen leading to erysipelas, and he achieved three remissions by injecting cultured living bacteria into seven cancer patients [16]. A few years later, Bruns, again using *Streptococcus pyogenes* cultures, reported 3 out of 5 cancer cures [6]. He already assumed that the high fever resulted in selective destruction of malignant cells. In 1891, Lassar failed to elicit tumor regression using a sterile culture filtrate of *S. pyogenes* that was not able to induce fever [25].

Thus, William Coley (1862–1936) was not the inventor of the treatment of cancer using bacterial infections. However, he was the first to do it systematically on a large number of patients. Coley, who lost his

first cancer patient despite radical surgery, systematically scanned patient records and medical literature at New York Hospital in the hope of finding hints as to how cancer might be better treated. He immediately came across the infection-remission coincidence, and it was, in particular, the combination of erysipela and sarcoma that excited him. In 1891, he treated a patient with a large, inoperable sarcoma of the neck by local injection of a broth culture of *S. pyogenes*. A severe attack of erysipelas from which the patient almost died led to complete remission within 2 weeks [11]. The patient survived 8 years, until he experienced a fatal relapse.

Coley soon recognized that it was sometimes not easy to control the infection (in the pre-antibiotics era the mortality from erysipela infection was about 10%), so he tried a heat-killed Streptococci vaccine. This attempt was similar to that of Lassar a few years before, and the result was similar also: non-live *Streptococci* bacteria did not show any therapeutic effect. He then added heat-killed *Serratia marrescens* (called *Bacteria prodigiosus* at his time) to the vaccine, because another investigator had published observations in rabbits indicating that the virulence of streptococcal cultures could be increased by *Serratia*. The addition of *Serratia* turned out to be crucial. This vaccine was able to cure 60 out of 210 terminally ill soft-tissue sarcoma patients (relapse-free survival more than 10 years after treatment) during his subsequent career [36]. Given this tremendous success, why has Coley's toxin never received a broader audience in the medical world?

There are four main reasons, which were all acknowledged by Coley himself. First, the vaccine appeared to work best with sarcoma patients, which represent only a small fraction of all cancers. Second, failures and successes did not show a clear pattern, which led Coley to try at least 13 different vaccine formulations over time and which, by the way, made it difficult to compare his case studies. Third was the concomitant development of radiation at the beginning of the century and chemotherapy in the forties, which provided much broader applicability and higher response rate (though not rate of curation), overshadowing Coley's work. Fourth, most of his experiments were done in a century in which medical wisdom almost completely denied any healing capacity of the human body with respect to cancer. For example, Professor Bauer, one of the founders of the German Cancer Research Institute (DKFZ) in Heidelberg, in his founding talk for the DKFZ in 1965, claimed that "the human body has no cancer fighting capabilities." This highly ignorant view was not substantiated even at that time, when hundreds of case studies of spontaneous remissions had been published. Even worse, we have to admit that this dogma was preserved in clinical standard therapy until the late 1980s, and we still find a majority of clinical oncologists who do not consider immunological measures. The persisting ignorance of clinical oncology towards the impact of a well-functioning immune system and the potential power of a stimulated immune response is one of the saddest examples of the occasional immobility of modern medical practice.

However, a more careful look may reveal that these four reasons for the small acceptance of the Busch-Coley therapy do not apply and that the principles behind Coley's successes have higher impact and broader applicability than a first glance might indicate. Coley's work was scrutinized in particular by two researchers: a daughter of William B. Coley, Helen Coley-Nauts, at the Cancer Research Institute, N.Y. [10], and Charlie O. Starnes from Amgen, Thousand Oaks, Calif. [41].

Coley himself felt that his vaccines worked almost exclusively in sarcoma patients, although at the very end of his life, considering the successes other contemporary physicians had using his vaccine, he stated that, "I had greatly underestimated the value of toxins in these (carcinoma) cases" [cited in 41]. Coley-Nauts, in the literature, found successful applications of Coley's vaccine by other surgeons in cases of metastatic breast carcinoma, recurrent malignant melanoma and metastatic ovarian cancer [10]. Starnes, after careful retrospective analysis, pointed out that the mesodermal embryonic origin of the cancers was the common denominator of the successful cases, which included sarcoma and lymphoma, as well as leukemia and carcinoma of renal, ovarian and other mesodermally derived tissues, rendering the fraction of treatable patients substantially larger than Coley realized.

Throughout Coley's career there were at least 13 different vaccine preparations in use, with different methods of production and therapeutic efficiency. Coley-Nauts, again after careful retrospective analysis of Coley's publications, found that three preparations were considerably more potent than the rest. These three preparations had the highest rate of curation (survival longer than 10 years) and were the most powerful in inducing febrile reactions. Effectiveness was also correlated with mode and duration of application of the vaccine. Although Coley, in his numerous publications, seldom gave full details of site, dosage, frequency, or duration of vaccine application, the optimal therapy regimen, with hindsight, seemed to be intratumoral, intramuscular or intraperitoneal high-dosage injections over long periods of time. Coley-Nauts end-result studies showed that 80% of inoperable soft tissue sarcoma patients survived 5–88 years if injections were given daily, or at least 2–3 times a week, irrespective of regression, for at least 6 months, with each injection raising the body temperature considerably for 12–24 h. Given that most of these cases were inoperable late-stage cancers, an 80% rate of curation is extraordinary. Caulkins, a contemporary physician achieved the same 80% survival rate with a similar 6- to 12-month vaccination regimen. Coley himself stated: "I feel that many of the past failures might have resulted otherwise had larger doses and more frequent injections been given" [10]. However, Coley did not sufficiently recognize the correlation between survival rate and induced fever temperature [30].

Table 1

Study	Treatment	Outcome	Remark	Ref.	Year
71 patients with inoperable metastatic neoplasms of different kinds, with different prior treatment by chemotherapy and radiation; 37 treated with CT vs. 34 with typhoid vaccine (control)	Coley's toxin	9 responses in CT, including 3 cures (no sign of residual tumor);1 slight response in control	Doses were increased in both groups until 102F was achieved; at least 10 injections were given; patients had different history of chemotherapy and radiation	[20]	1962
93 patients with inoperable metastatic neoplasms of different kinds, all treated by CT	Coley's toxin	18 responses including 1 cure	Doses were increased in both groups until 102°F was achieved; at least 10 injections were given; patients had different history of chemotherapy and radiation	[21]	1962
52 patients with reticulo sarcoma	MBV (47 patients)	5-year survival 64% (compared to historical rate of 30–40%)	Doses were adjusted to induce a minimum level of temperature	[28]	1971
8 patients with refractory malignancy, who had progressed beyond standard therapy, were treated with MBV only; 4 patients with non-small cell lung carcinoma were treated with MBV plus chemotherapy; 2 patients with non-small cell lung carcinoma were treated with chemotherapy only	MBV	No end-point defined. One patient of group one with prior leukemia and leyomyosarcoma was alive two years after MBV treatment with stable disease	MBV-safety study. No attention was given to level of fever induced; number of MBV treatments was low	[3]	1988
15 patients with malignant melanoma	Vaccineurin	3 remissions lasting at least 15, 21 and 32 months	One injection per week, up to 12 weeks. Attention was given to reach a body temperature of at least 39 °C per injection	[23]	1991
86 patients with hepatocellular carciinoma (group 1: 38 with prior resection and chemotherapy; group 2: 48 with prior radiation and chemotherapy)	MBV for half of each group	2 year survival rate (MBV vs. control) 45% vs 39% in group 1 and 41% vs. 25% in group 2		[38]	1991
11 patients with refractory disease and prior treatment by chemotherapy and radiation treated by MBV	MBV	4 patients classified as "disease stabilized", plus 2 patients with response	Number of vaccinations ranged from 3–122, one breast cancer patient (122 vacc.) had complete disappearance of bone pain, could walk again and died 507 days after begin of treatment due to unrelated cause	[19]	1993
Meta-analysis of over 1520 patients with resected non-small-cell lung cancer enrolled in 11 clinical trials; control was chemotherapy alone	Picibanil	5-year survival rate was 51.2% for Picibanil plus chemotherapy vs. 43.7% for chemotherapy only control	No coherent attention given towards height and duration of fever induction	[35]	2001

After the tragedy of thalidomide in 1963, very stringent regulations regarding clinical trials of new drugs were installed by the FDA. Although Coley's toxins were 70 years old, the Kefauver Act decided it was a new drug requiring special permission. Therefore, a novel formulation of bacterial toxins was developed, which is called mixed bacterial vaccine (MBV) and has less adverse side effects [19]. In recent years, Coley's toxin and MBV have been tested again in a few clinical trials in an attempt to scrutinize the drug by applying higher scientific standards compared to Coley's time (see Table 1). In all those studies, no selection for patients with cancers of mesodermal origin was performed. In most studies using MBV, a few injections were given over short periods of time, paying no attention to the correlation between length of treatment and severity of fever induced, on the one hand, and effectiveness, on the other, which is apparent from Coley's experiments. Most of the patients in Table 1 were late-stage cancers, most of them treated previously by chemotherapy and radiation without success. Since these prior treatments might reduce the efficacy of Coley's toxin due to their immune-compromising effects, and since late-stage cancers are particularly difficult challenges, the few responses and even cures reported might be, in fact, a surprisingly favorable outcome.

Richardson et al. [33] tried to match 128 Coley cases with 1,675 controls from the Surveillance Epidemiology End Result (SEER) population-based cancer registry. Groups were matched on age, sex, ethnicity, stage and radiation treatment status. The results are summarized in (Table 2).

The authors state: ''Given the tremendous advances in surgical techniques and medicine in general, any cohort of modern patients should be expected to fare better than patients treated 50 or more years ago. Yet no such statistical advantage for the modern group was observed in this study.''

Concurrence of fever and spontaneous remission

Cautious physicians, in their bedside practice, sometimes recognized beneficial fever effects. In 1950, Shear reported that brief remissions in children with untreated leukemia were observed in about 10% of the patients. Three quarters of those remissions were preceded by an episode of acute infection. In a remarkably lucid statement, he wrote: ''Are pathogenic and non-pathogenic microorganisms one of Nature's controls of microscopic foci of malignant tissue, and, in making progress in the control of infectious diseases, are we not removing one of Nature's controls of cancer?'' [32].

Table 2

Median survival in years (number of patients) Cancer type	Coley	SEER
Kidney	6.5 (6)	5.0 (13)
Ovarian	10.0 (9)	8.0 (47)
Breast	5.0 (24)	7.0 (1561)
soft tissue	10.0 (89)	8.0 (54)

Literature surveys on spontaneous remissions and regressions, including the reviews of Everson and Cole [14], Boyd [5], Stephenson et. al. [37], Challis and Stam [8], and Maurer and Kölmel [27], covered more than 700 case studies of spontaneous regression, and all authors underlined the coincidence of spontaneous regression and feverish infection, which occurred in at least a quarter of cases [27, 37].

One might speculate that the sex-specific incidence of bladder cancer, which is four times lower in women than in men, could possibly be caused by the more frequent bladder infections in women due to a shorter urethra. Furthermore, Kölmel et al. [22], who compared the history of severe infections in 603 melanoma patients with that in 627 population controls, found inverse correlations between melanoma risk and number of recorded infections, and between melanoma risk and fever height, leading to a combined reduction of melanoma risk of about 40% for people with a history of three or more infections with fever above 38.5 °C. The observation that cancer patients very often report long-lasting periods without any disease may also provide some insight [1, 13].

An immunological hypothesis

The effects of the Busch-Coley treatment and the frequent concurrence of spontaneous remissions with fever might both be explained by the following hypothetical cascade of events: fever generates inflammatory factors with co-stimulatory activity, which activate resting dendritic cells (DC), leading to the activation of anergic T-cells, maybe accompanied by a second process, where a possible physical damage of cancer cells leads to a sudden supply of cancer antigens to DC.

It has been known for a long time that in many cancer cases a T-cell response occurs, but cancer-cell-specific T-cells usually remain in a state of anergy, most likely because of the absence of danger signals that accompany tissue destruction and inflammation upon (e.g.) infection, i.e., T-cells remain anergic due to a lack of co-stimulatory signals [31]. Potent co-stimulatory signals (e.g., B7, IL-12) are expressed by antigen-presenting cells (APC), in particular DC. Resting DC can be activated by a number of stimuli, including: lipopolysaccarides (LPS), contact allergens, bacterial and viral products, products from necrotic cells, TNF-alpha, IL-1beta, PGE2, unmethylated CpG tracts in DNA and signalling molecules like CD40. A feverish bacterial infection may have a three-fold beneficial effect. First, many infectious agents release endotoxins, like LPS, and induce inflammatory cytokines, stimulating DC. Second, both thymocyte proliferation and generation of allo-specific CTL are increased with temperature in vitro [18]. Third, cancer cells may be less heat-resistant than

normal cells [39] and, consequently, fever may cause an increase in tumor-cell death and the production of tumor-cell debris. This latter effect may also be produced by hyperthermia [15, 39]. DC can be activated by antigen-carrying dying cells [2], where death may be mediated both by apoptotic [9] and necrotic [17] pathways. Activation of DC might lead to subsequent activation of cytotoxic T-lymphocytes (CTL), perhaps in some cases leading to a full-blown attack against antigen-carrying cancer cells.

The antigenicity of tumor antigens depends on whether the antigens are highly tumor-specific or whether they are shared by other body tissues. Almost exactly 100 years after Coley's seminal experiments, Srivastava and co-workers found a hint as to why sarcoma might be particular. They determined that membrane-bound heat-shock proteins complexed to tumor peptides as powerful antigens on sarcoma cells [40]. Soon afterwards, Multhoff et al. showed that physical (non-lethal) heat shock results in an increased cell-surface expression of Hsp70 heat-shock protein on sarcoma and lymphoma cell lines [29]. It would be interesting to know whether this behaviour extends to other cancers of mesodermal origin. Certain carcinoma cell lines exhibit this unusual Hsp70 cell-surface expression even under normal physiological conditions [4]. Although the carcinoma stress-independent membrane expression of Hsp70 corresponds with an increased sensitivity to lysis by natural killer (NK) T-cells in vitro [4], the situation in vivo may be different. As Pardoll pointed out, immunological kinetics may be crucial: full-blown T-cell activation by DC may require the presence of co-stimulatory signals at the time of *first* antigen recognition [31], perhaps leading to the alleged higher efficiency of fever therapy with sarcoma compared to carcinoma.

Conclusion

A huge body of scientific literature indicates that the immune system can sometimes be a very powerful weapon against cancer. As yet, there is no modern clinical study with cancer patients treated by MBV aimed at optimizing patient selection and treatment protocol, namely, selecting for patients with cancers of mesodermal origin and treatment for long periods of time, beginning at a very early stage of the disease. Treatment might be combined with strategies to block inhibitory pathways of T-cell activation temporarily, e.g., blockade of CTLA-4 [24] by an anti-CTLA-4 antibody [26] or blocking FASL-FAS interactions [34].

Immune strategies targeting unique tumor-specific antigens should be individualized rather than generic, and fever induction is, by necessity, a means of inducing an individualized response. Today, we can induce and control fever much better than 100 years ago, we have a much better understanding at the molecular level, and we have a plethora of additional immune-stimulators available, which might be combined into a synergistic therapy regimen. It is time to scrutinize fever therapy again.

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