

REVIEW

Fever in Cancer Treatment: Coley's Therapy and Epidemiologic Observations

Gunver S. Kienle, Dr med

Author Affiliation

Gunver S. Kienle, Dr med, is senior research scientist at the Institute for Applied Epistemology and Medical Methodology at the University of Witten/Herdecke in Freiburg, Germany.

Correspondence

Gunver S. Kienle, Dr med
gkienle@gahmj.com

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In the fall of 1890, an athletic, self-possessed, and thoughtful 17-year-old girl, who had just returned from an adventurous trip to Alaska where she had hurt her hand in a trivial accident, went to see a young, innovative surgeon in his new practice in New York City. Barely out of Harvard Medical School, he was a rising star in New York surgical circles, and the young woman asked him for help with her poorly healing, swollen, and naggingly painful injury. This visit had a far-reaching effect on cancer research, American philanthropy, and the career of the young man, William Coley, MD (1862-1936, Figure 1). The patient, Elisabeth Dashiell, confidant and close friend of John D. Rockefeller, Jr, was diagnosed by Coley with a highly aggressive round cell sarcoma, and despite radical surgery and in spite of Coley's undoubtedly fine surgical skills and intensive care, a rapid progression of the cancer, immense suffering, and Elisabeth's death a few months later could not be prevented.

The experience of the swift, fatal course and of the insufficiency of surgery in even the finest and most modern American hospital left Coley deeply shaken—and determined to find a treatment for this dreadful disease. It also was the starting point of Coley's lifelong friendship with Rockefeller, whose philanthropic work was inspired by Elisabeth's death, leading to the foundation of the Rockefeller University.¹

Coley went on to develop the first immunological cancer treatment, attempting to cure cancer with fever, and thereby founded the field of tumor immunology. He began with an investigation of all case histories of sarcoma at the New York Cancer Hospital (later Memorial Sloan-Kettering). He stumbled on the record of 31-year-old Fred K. Stein, who was afflicted with a round cell sarcoma on the neck that had recurred 5 times after surgical removal until it was considered inoperable; the case had been declared hopeless when the man contracted a severe erysipelas infection (caused by *Streptococcus pyogenes*) that spread rapidly over the neck and face and was accompanied by a raging fever. A second attack followed 2 weeks later. In the course of these attacks, the sarcoma disappeared entirely. Seven years later, Coley tracked Stein down on the Lower East Side, where he still enjoyed excellent health and had only a scar below his ear left to show where the "inoperable" sarcoma had been.^{1,2}

FEVERISH INFECTIONS AND SPONTANEOUS REMISSION

Since the 18th century, spontaneous remissions of cancer—altogether a very rare event—have been



Figure 1 William Coley, circa 1888, at the start of his medical career. Reprinted with permission from the Cancer Research Institute.

observed repeatedly in connection with febrile infectious diseases, especially those of bacterial origin.^{1,3-5} In 1866, Busch described complete remissions occurring under erysipelas covering the tumor.³ In 1882, Fehleisen induced tumor remission with the inoculation of streptococci causing erysipelas.⁶ The French physician Dussosoy dressed an ulcerated breast carcinoma with charpie soaked with gangrenous discharge and inoculated gangrenous matter; the tumor was said to have disappeared.⁴ In the 1950s, Huth described 24 remissions of leukemia after bacterial infections.⁷ Of a total of 224 spontaneous remissions of cancer reviewed by Stephenson, 62 had occurred under infection or persistent fever and 77 under "reticuloendothelial stimulants."⁸ Of 68 spontaneous remissions of metastatic melanoma, 21 occurred concurrent to infections and 11 to immunoactive interventions (eg, vaccination, application of antibodies, tumor cells, Bacillus Calmette-Guérin [BCG]).⁹ Of 86 spontaneous remissions of lymphoma, 3 occurred after bacterial or viral infections and 12 after termination of immunosuppressive treatment.¹⁰ Of 98 children with Hodgkin's lymphoma, 3 contracted measles that led to tumor remission.¹¹ Among 21 patients with spontaneous regression of colorectal cancer, 6 occurred under septic complications or febrile

pneumonia.¹² A profound and comprehensive documentation included 449 cases of spontaneous or induced bacterial or viral infections in cancer patients that led to remission in most cases. For instance, of 163 patients with inoperable carcinoma or sarcoma who had pyogenic infections, a complete regression had occurred in 37 who were followed for 5 to 46 years; in 54 patients, the tumor had regressed completely but was followed for less than 5 years or diagnosed only clinically; 13 patients had shown no response; the remaining patients had a tumor remission with an unknown long-term outcome or had died.¹³

Coley thoroughly reviewed the literature available at that time and found 38 reports of cancer patients with accidental or iatrogenic feverish erysipelas. In 12 patients, the sarcoma or carcinoma had completely disappeared; the others had substantially improved. Coley decided to attempt the therapeutic use of iatrogenic erysipelas when the next patient with an infaust and hopeless condition was referred to him: Signor Zola, a 35-year-old Italian, had a recurrent and now inoperable sarcoma of the neck and the tonsil (Figure 2). The size of a hen's egg, it almost completely blocked the pharynx. The patient was in a bad condition—cachectic, with liquids regurgitated through the nose—and was expected to live only a few weeks. Coley inoculated *Streptococcus pyogenes* every 3 to 4 days for months but only induced slight local and systemic reactions, leading to some tumor shrinkage and improvement of the general condition but not to erysipelas or to disappearance of the tumor. When the inoculations were paused, the tumor continued to grow and shrank again during the next inoculations. Dissatisfied with this course, Coley managed to get bacteria from Robert Koch's laboratory in Germany. Within 1 hour of the bacteria being injected directly into the neck tumor, the patient developed chills, pain, nausea, vomiting, and a high fever (105°), and after 12 hours, a typical erysipelas stretched over the tumor of the neck, extended over the face and head, and met on the other side. The attack lasted 10 days. The neck tumor changed promptly, got paler and softer, began to break down on the second day, discharged a caseous material until the last day, and had disappeared after 2 weeks. The tonsil tumor regressed but never disappeared completely and remained as a hard, fibrous mass. The patient rapidly gained strength and appetite and became perfectly well again for 8 years. The tumor then recurred, and he died of the disease.^{2,14}

Coley treated with living bacteria 10 patients who had inoperable sarcoma (n=6) or carcinoma (n=4) and infaust prognoses. Repeatedly, the condition temporarily improved and the tumor partly regressed, but no erysipelas could be induced. Just 4 patients developed a full erysipelas, followed by a remission of the tumor.² However, 2 additional patients died due to erysipelas infections that raged out of control.^{1,2}

MIXED BACTERIAL VACCINE

Different lessons were learned: A fulminant attack



Figure 2 Signor Zola, who survived another 8 years after being treated by Coley in 1891.

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of erysipelas can induce dramatic and complete tumor remission; a mere injection of *Streptococcus pyogenes* without a full erysipelas can improve the disease and induce some tumor shrinkage but does not lead to complete, durable tumor remission; it is not easy to induce a full erysipelas attack by streptococci; and erysipelas is a severe, life-threatening disease. These difficulties led Coley to try cultures sterilized by heating or filtration, which produced little effect. Inspired by the animal experiments of Rogers, he mixed them with toxins of gram-negative *Serratia marcescens* and thus created the mixed bacterial vaccine (MBV). The first patient treated with MBV was a 16-year-old German with an inoperable spindle cell sarcoma on the abdominal wall, 6.5 x 5.25 x 5 inches, attached to the pelvis, and infiltrating the bladder. The patient was in bad condition when the MBV treatment was started. The intratumoral injections were followed by a temperature increase of 0.5° to 6°, with tachycardia, chill, extreme trembling, and severe headache. At times, the tumor was enlarged on the days following the injection but then gradually decreased over the next months and finally disappeared. The man regained good health and stayed healthy without a recurrence until he suddenly died of myocarditis 26 years later in a subway station.¹⁵

Coley, who meanwhile became a staff member and later chief of the Bone Cancer Department of the New York Cancer Hospital—the second in the world dedicated to the treatment of cancer and supported by wealthy families¹⁶—successively developed and improved MBV treatment, the first official immunotherapy for cancer. Especially in sarcomas but also in other cancer types, long-term remissions could be

TABLE 1 Patients With Inoperable Cancer Treated With Mixed Bacterial Vaccine Alone Before 1940^a

Type of Cancer	Total	Patients With Complete Tumor Remission				No Tumor Response
		Follow-up				
		> 20 y	10-20 y	5-10 y	< 5 y ^b	
Soft tissue sarcomas	84	17	12	11	12	32
Lymphosarcomas (lymphomas)	33	8	7	4	4	10
Osteosarcoma	3	0	0	0	1	2
Ewing's tumor/reticulum cell sarcoma	1	1	0	0	0	0
Ovarian carcinoma	4	1	0	0	2	1
Cervical carcinoma	2	1	0	0	1	0
Testicular tumor	14	1	2	3	3	5
Renal tumor	8	1	1	1	1	4
Multiple myeloma	1	0	0	1	0	0
Colorectal carcinoma	1	0	0	0	0	1
Breast carcinoma	13	0	0	2	6	5
Melanoma	6	0	1	0	3	2

^a Values indicate number of patients with or without tumor response, duration of follow-up with no indication of relapse.¹⁷

^b Or relapse within 5 years.

achieved with MBV alone, without surgery or radiotherapy (Table 1).¹⁷

The patients were tracked down, and their long-term outcomes were carefully documented over years and decades, up to 88 years in one case. The documentation was done for the most part by William Coley's daughter, Helen Coley-Nauts (1907-2000), founder of the New York Cancer Research Institute. She conscientiously and comprehensively documented all the patients treated with MBV by her father and colleagues and tried to keep track of all of them. In 1953, she published her first detailed analysis, which attracted worldwide attention. She had collected 1200 cases treated with MBV and reported more than 270 patients with inoperable cancer achieving a complete remission with MBV; the follow-up time stretched up to 45 years. Cases were classified into "successes" (ie, complete remission with no recurrence during later years) and "failures": those cases that also included complete remissions but in which cancer recurred later.

In 1959, a survey was published on all MBV-treated cases with soft tissue sarcoma (except lymphosarcoma) known to the New York Cancer Institute. Of 186 patients, in 105 (57%), the treatment was regarded as successful (of these, 35 tumors were operable and 70 tumors were primarily inoperable, 2 of which were treated with apparent success with radiotherapy), with a follow-up of 4 to 62 years (one of the patients was pregnant; she later gave birth to a healthy baby). Eighty-one (43%) patients were treated "unsuccessfully," which included patients with complete tumor remissions that later relapsed.^{18,19} Other surveys assessed and described MBV treatment in reticulum cell sarcoma of the bone²⁰; Hodgkin's lymphoma²¹; osteogenic sarcoma^{22,23}; ovarian, uterine, and cervical carcinoma²⁴; breast cancer²⁵; neuroblastoma²⁶; renal cancer²⁷; melanoma²⁸; testicular cancer²⁹; sarcoma

of the soft tissues³⁰; colorectal cancer³¹; Ewing's sarcoma³²; and multiple myeloma³³ with similar results.

MBV was usually injected intramuscularly and locally intra- or peritumorally; intravenous application was not generally recommended due to safety concerns. Patients developed shaking chills followed by fever (102-105° F) lasting up to 12 to 24 hours. The injections were repeated first every day and then on alternate days with increasing dosage. High and consistent fever plus the local inflammation at the tumor site were regarded as essential for therapeutic success. Treatment success was obvious within a few days: the tumors became paler, softer, and movable, then regressed or opened and discharged a caseous secretion or just regressed. If these reactions did not occur within 1 to 4 weeks, MBV was regarded as ineffective; nevertheless, it often still improved the patient's general condition, reduced pain, or improved appetite. To achieve a durable remission and prevent relapses, the treatment was continued for a long time (usually months).^{34,35} Patients were treated according to their individual constitution and reaction in order to increase the effectiveness and to minimize the risks.^{34,35} The recurrent chills and the induced fever over weeks and months were strenuous for the patients, many of whom were severely ill. In 1000 treated patients, 6 fatal complications were observed due to embolism, acute nephritis, hemorrhage (if the tumor had grown into a blood vessel), or the injection of too large initial dosages by inexperienced physicians.^{34,36,37} Otherwise, MBV was largely safe.^{18,19,38-40}

Up to 15 different preparations of MBV existed, but not all were potent enough to induce high fever and durable remissions.^{30,41} This was particularly the case with the commercial preparations used mostly outside of New York. In one instance, Coley was contacted by a colleague who had treated a lymphosarco-

ma patient with high doses of a commercial product without any response. When Coley provided him with vaccines from his own supply, the patient reacted to the very first injection with high fever, chills, and subsequent tumor remission and was disease-free until he died of heart disease 33 years later.³⁰

After Coley's death in 1936, MBV treatment was continued but clinical interest diminished in favor of radiotherapy and chemotherapy, which promised a breakthrough in cancer treatment comparable to antibacterial treatment. In 1961, the thalidomide tragedy occurred and gave rise in the United States to the Kefauver Harris Amendment, which applied strict requirements to preclinical and clinical investigations of new treatments. Although it had been used for 70 years, MBV was at that time classified as a new treatment, necessitating expensive investigations for drug licensing. As MBV is a natural substance and was therefore not patentable, the investment of millions of dollars for testing was unattractive for any drug company. As for academic institutions, other topics were more appealing than an old bacterial treatment dealing essentially with "dirt."

Still, some small prospective studies were conducted; MBV treatment was, however, increasingly standardized, applied less aggressively, and the vaccines less potent (Helen Coley-Nauts, oral communication, December 1996). Furthermore, the included patients were often pretreated with chemotherapy or radiotherapy, which substantially alters the immune system and therefore modifies the response to an immunomodulating treatment.¹⁷

In one randomized controlled trial (RCT), MBV-treated patients with advanced, metastatic cancer (n = 34) showed 7 subjective and 9 objective responses, 3 of which were complete remissions (partly verified by later autopsy); in the control group (n = 37), which was administered typhoid vaccines, one improvement was reported.³⁸ Of 93 patients with advanced cancer in a single-arm MBV study, 30 had a tumor remission (partly verified by later autopsy), 20 reported subjective improvements, and the remaining 43 had no change.³⁹ In a study of 7 patients with inoperable cancer, no remissions were found.⁴² In a small RCT, patients with advanced non-Hodgkin's lymphoma who were treated with MBV in addition to chemotherapy showed higher response rates than control patients without MBV (complete remissions 85% vs 44%, respectively), and survival was significantly longer.⁴³⁻⁴⁵ Patients with liver cancer showed better survival (trend) in an RCT when chemotherapy (partly also radiotherapy) was combined with MBV.⁴⁶ In a study on metastatic melanoma, of 15 patients receiving MBV, 3 had a complete remission (20%) lasting at least 15, 21, and 32 months.³⁹ Other studies on MBV primarily investigated immunomodulation and tolerability.^{47,48} Recently, 128 cases treated with MBV between 1890 and 1960 were matched with 1675 control patients from the Surveillance Epidemiology End Results (SEER) cancer

registry who received a cancer diagnosis in 1983. The survival rates were not significantly different, despite the tremendous advances in surgical techniques and modern medicine with which patients in the SEER group were treated (Table 2).⁴⁹

TABLE 2 Survival of Patients Treated (1890-1960) With Mixed Bacterial Vaccine (MBV) Matched With Patients From Surveillance Epidemiology End Results (SEER) Diagnosed in 1981^a

Tumor type	Median Survival, y		10-y Survival Rate	
	MBV	SEER	MBV	SEER
Kidney cancer	6.5	5	33.3%	23.1%
Ovarian cancer	10	8	55.6%	29.8%
Breast cancer	5	7	25.0%	38.1%
Soft-tissue sarcoma	10	8	50.6%	38.9%

^a Matching criteria: site, stage, treatment status (ie, no radiotherapy), age, sex, ethnicity.⁴⁹

INFECTIOUS DISEASES AND SUBSEQUENT CANCER

Clinicians frequently have claimed that the anamnesis of cancer patients revealed fewer feverish infections compared to other patients. This gave rise to numerous epidemiological investigations,⁵⁰ which predominantly show an inverse association between various acute infectious diseases or fever and cancer risk (Table 3).⁵¹⁻⁸⁸ The risk is further reduced with increased frequency of infections and if fever is involved. Somehow, these events affect cancer immune surveillance, which seems to be—conversely—negatively affected by the risk factors supporting cancer growth.⁸⁹

Often, a better outcome is also reported in cancer patients who had postoperative infections. However, the corresponding studies usually refer to very small sample sizes, limiting their validity. Potential confounders prevalent especially after postoperative infectious complications are another reason for these altogether conflicting results. For instance, several studies reported longer survival in patients with empyema after lung cancer surgery.⁹⁰⁻⁹³ These observations prompted an RCT in which BCG was applied intrapleurally after resection of lung cancer, which led to a substantial reduction of recurrences in early stages but no difference in advanced stages of the cancer.⁹⁴ Two studies found no difference in survival after empyema,^{95,96} and one study showed a slightly negative effect.⁹⁷ In colon cancer (stage I), one study found better survival in patients with postoperative infections,⁹⁸ another study found no difference,⁹⁹ and a third study found increased recurrences (with, however, an altogether high prevalence of infections).¹⁰⁰ In melanoma, after local wound infection, decreased recurrences were reported, but there was no difference in survival.¹⁰¹ Survival also was increased in osteosarcoma patients after postoperative infection.¹⁰² In patients with breast and head and neck cancer, however, rates of recurrence were higher and survival partly reduced after a postoperative increase in temperature or wound infection.¹⁰³⁻¹⁰⁵

Interestingly, in contrast to acute inflammation,

TABLE 3 Epidemiologic Studies (One Meta-analysis) Investigating the Association Between Infectious Diseases and Subsequent Cancer^{51-88,a}

Infectious Disease or Condition	Case/Control	Cancer Site	History of Infectious Diseases in Cancer Patients/ Cancer Risk After Infectious Diseases	Year	Reference No.
Childhood disease, infectious diseases	241/—	Gastrointestinal	No infectious disease as child in 180 patients, as child and as adult in 99 patients	1910	51
Childhood disease, infectious diseases	300/300	Multiple	No infectious disease in 113 cancer patients vs 16 control patients	1934	52
Childhood disease, infectious diseases	232/2444	Multiple	Fewer infectious diseases, especially childhood diseases	1936	53
Tonsillectomy ^a	831/9990	Upper aerodigestive tract	Fewer tonsillectomies	1960	54
Tonsillectomy ^a	542/5020	Upper aerodigestive tract	Fewer tonsillectomies	1963	55
Mumps, measles, rubella	97/97	Ovarian	Less mumps and rubella	1966	56
Mumps	36/150	Ovarian	No association	1969	57
Typhoid fever	5460 ^b / Viennese population	Multiple	Lower cancer mortality in survivors of typhoid fever 1945-1947	1970	58
Multiple (febrile disease, other diseases)	150/150	Multiple	Less fever (1% vs 13%), fewer doctor visits (15% vs 45%), less hospitalization (5% vs 12%)	1970	59
Pneumonia, influenza	399/395	Ovarian	Less pneumonia and influenza	1974	60
Tonsillectomy ^a	305/305	Leukemia (in children)	Fewer tonsillectomies	1975	61
Tonsillectomy ^a	752/752	Leukemia	Fewer tonsillectomies	1976	62
Mumps, measles, chicken pox, rubella	300/600	Ovarian	Fewer infections (reduced risk of ovarian cancer in history of infections: RR 0.47-0.86)	1977	63
Tonsillectomy ^a	1415/1415	Lung	Fewer tonsillectomies	1978	64
Rubella, measles, mumps	197/197	Ovarian	Overall, no difference; more peripubertal rubella and measles (12-18 y), less during childhood years	1979	65
Immunizations, infectious diseases	33/99	Rhabdomyosarcoma (in children)	Fewer immunizations, more preventable (with immunization) infectious diseases	1982	66
Multiple, fever	110/126	Multiple	Less fever, fewer colds and organic infections	1983	67
Measles	252/230 ^c	Multiple	More tumors in people with no measles rash despite immunoglobulin G measles antibody	1985	68
Multiple	492/480	Leukemia (in children)	Reduced risk of leukemia after serious infectious diseases: RR 0.6	1986	69
Common cold	120/239	Multiple	No association	1986	70
Fever >3 days, herpes	204/1353 ^d	Multiple	Reduced cancer risk after febrile diseases	1987	71
Multiple	255/485	Multiple	Reduced cancer risk after cold/influenza (OR 0.18-0.23) or febrile abdominal influenza (OR 0.15-0.23) but not after childhood diseases	1991	72
Childhood disease, febrile infectious diseases	139/271	Melanoma	Reduced risk of melanoma after chronic infectious diseases (OR 0.32), febrile abscesses, wound infections (OR 0.21), influenza/cold (OR 0.32), trivial febrile diseases (OR 0.34). No association with childhood disease	1992	73
Chicken pox, shingles	462/443	Glioma	Fewer chicken pox (OR 0.4) and shingles (OR 0.5)	1997	74
Febrile childhood disease	379/379	Multiple	Reduced cancer risk after febrile childhood diseases (non-breast cancer OR 0.27, especially rubella, chicken pox)	1998	75
Infectious diseases	Italian population	Multiple	Decreased mortality from infectious diseases (1895-1947) paralleled and followed by increased mortality from cancer (1895-1990)	1998	76
Multiple (severe or less severe, fever)	603/627	Melanoma	Reduced risk of melanoma after febrile infections: tuberculosis (OR 0.16), Staphylococcus aureus (OR 0.54), sepsis (OR 0.23), flu (OR 0.65), pneumonia (OR 0.45); dose-response relationship	1999	77
Infectious diseases	1509/2493	Glioma, meningioma	Reduced risk of glioma and meningioma after infectious diseases (RR 0.72 and 0.73)	1999	78

TABLE 3 Epidemiologic Studies (One Meta-analysis) Investigating the Association Between Infectious Diseases and Subsequent Cancer^{51-88,a} (cont)

Infectious Disease or Condition	Case/Control	Cancer Site	History of Infectious Diseases in Cancer Patients/ Cancer Risk After Infectious Diseases	Year	Reference No.
Childhood disease, febrile infections	111/109	Multiple	Increased risk of cancer after mumps, whooping cough, decreased risk after cold	2002	79
Childhood disease, ear infection	538/504	Neuroblastoma (children)	Reduced risk of neuroblastoma after childhood diseases (OR 0.60), increased risk after ear infections (OR 1.76)	2004	80
Infections	455/1031	ALL (children)	More infectious episodes in leukemia than control patients (3.6 vs 3.1)	2007	81
Infections	162/2125	Leukemia (children)	No association	2008	82
Vaccination, childhood disease	399/399	Leukemia (children)	No association	2008	83
Fever during infections, childhood disease	355/244	Multiple	Less mumps, rubella, chicken pox. Never fever in 83% of cancer vs 57% of control patients	2009	84
Day-care attendance ^e	6108/19910 ^f	ALL (children)	Reduced risk for ALL (OR 0.76) after day-care attendance	2010	85
Common infections, day-care attendance ^e	720/1494	ALL, acute myeloblastic leukemia (children)	Reduced risk for ALL after repeated common infections (OR 0.7) and day-care attendance (OR 0.8)	2010	86
Tonsillitis, tonsillectomy ^{a,g}	2988 ^h	Hodgkin's lymphoma	Increased risk (RR 1.4) of lymphoma after tonsillitis	2010	87
Common infections, day-care attendance ^e	669/977	ALL (children)	Reduced risk of ALL after day-care attendance and ear infections	2011	88

Abbreviations: ALL, acute lymphoblastic leukemia; OR, odds ratio; RR, relative risk.

^a Tonsillectomy as indicator for tonsillitis.

^b Exposed to typhoid fever.

^c Negative vs positive history of measles.

^d Total patient group (prospective study).

^e Day-care attendance as indicator for early exposure to various infectious diseases.

^f Meta-analysis of 14 studies.

^g Studies on tonsillectomy only partly included.

^h 124 million person years.

chronic inflammation increases cancer risk and can affect every aspect of tumor development.¹⁰⁶ Many chronic viral, bacterial, and parasitic infections are a risk factor for developing cancer: *Helicobacter pylori* in mucosa-associated lymphoid tissue lymphomas, Epstein-Barr virus in lymphoma or nasopharyngeal cancer, hepatitis B and C virus in liver cancer, herpes virus type 8 in Kaposi sarcoma, human papillomavirus in cervix or anogenital cancer, *Schistosoma* in bladder cancer, and others.⁵⁰ About 15% to 20% of cancers worldwide are attributed to these infectious agents.¹⁰⁷ Noninfectious chronic inflammatory diseases also are a major risk factor for cancer. Examples include inflammatory bowel disease and colon cancer, bronchitis and lung carcinoma, reflux esophagitis and esophageal cancer.^{106,108} Sustained inflammation seems to be the result of an individual's inability to eliminate infection and restore immune homeostasis.^{50,109} Immune and inflammatory cells as well as cytokines can have anti-tumor- and tumor-promoting functions, depending on the context.^{106,110,111}

INITIATION OF CANCER IMMUNOTHERAPY

In Coley's era, the scientific and medical community lacked the prerequisite knowledge to understand his treatment. The intellectual environment was incapable of making scientific sense of tumor remissions after application of bacterial toxins. Hardly anything was known about the immune system. The notion of cellular immunity was completely out of favor.

Regarding inflammation, almost everybody agreed that this was a deleterious reaction of no benefit for the host, a purely passive response to the insulted organism.¹¹² So it is not surprising that Coley—a respected surgeon but not a trained scientist—received harsh opposition.¹ For decades after Coley's death, fighting cancer with a host response was regarded as impossible; for a long time, investigating tumor immunity was considered a scientific red-light district, "a seedy intellectual neighborhood of fantasy and wishful thinking, a landscape littered with the hulks of abandoned hypotheses and charred reputations." It was a biological minefield, capable of ruining careers.¹ Even in the 1980s, the concept of clinical tumor immunity was regarded as consisting of laboratory artifacts.¹¹³⁻¹¹⁵

Still, Coley's work substantially inspired research, and his observations were a main impulse for later tumor immunology. Shortly after Coley's death, Shear discovered lipopolysaccharides (LPS), a component from the membrane of *Serratia* that induced necrosis of sarcoma in mice.¹¹⁶ Later, Old and Carswell isolated tumor necrosis factor (TNF) as an active mediator in LPS- or BCG-induced tumor necrosis.^{117,118} These and other discoveries restored Coley's reputation. They were considered to provide a satisfactory answer to his observations,^{118,119} but despite all expectations, the cures obtained with MBV could not be replicated with isolated TNF- α or other cytokines. Nevertheless, these discoveries marked the beginning of an immunological

renaissance in cancer research and assured Coley a permanent place in history.¹²⁰

Today, a far more comprehensive understanding of the human immune system and tumor immunology is present,¹²¹ as is a conceptual extension beyond the simple self-nonsel model,¹²² permitting a better understanding of Coley's results. Obviously, MBVs stimulated a complex cascade, a "perfect storm" of cytokines—among these, interleukin (IL)-2, interferon- α ,¹²⁰ TNF- α ,^{118,119} and IL-12¹¹⁹ are seen as critical—and of toll-like receptors and other pattern recognition receptor agonists, each of which plays a unique and vital role in the orchestration of the immune response.¹²⁰ Both the innate and the adaptive immunity are decisive, and the tumor vasculature is involved.^{17,120} Critical in the mediation of MBV effects is probably the activation of resting dendritic cells—via induction of cytokines and inflammatory factors with co-stimulatory activity. This leads to an activation of anergic T-cells, paralleled by a possible direct damage of cancer cells, inducing an improved supply of tumor antigens.¹²³

A growing body of literature shows the complex modifying and orchestrating effects of fever and elevated temperature on the host response, immune cells, cytokines, antimicrobial defense, antitumor activity, and immune surveillance.¹²⁴⁻¹²⁷ For instance, fever and hyperthermia activate the heat-shock response, inducing heat-shock proteins; these can then activate dendritic cells and transform them into mature antigen-presenting cells, which then potentiate the immune recognition of antigens. Furthermore, hyperthermia improves immune surveillance by activating NK-cells and T-cells and increasing trafficking of dendritic cells into lymph nodes.¹²⁷ Hyperthermia also directly induces tumor cell necrosis and apoptosis.¹²⁸ In patients with sarcoma, hyperthermia increases the antitumoral efficacy of chemotherapy and radiotherapy.^{129,130}

It is notable that erysipelas in particular is connected with spontaneous or induced tumor remission. Heat-killed, however, these gram-positive bacteria are hardly effective at all. In MBV, the gram-negative *Serratia* far outweigh the streptococci by an estimated factor of 7300:1, and in animal experiments, the curative and toxic effects are connected to *Serratia* whereas heat-killed streptococci alone are neither therapeutic nor toxic. Additionally, further research centered on endotoxins that are not present in gram-positive streptococci. During a fulminant erysipelas attack, possibly, a translocation of endotoxins of the gastrointestinal tract is induced, which then initiates a cytokine cascade.¹⁷ A further influence might be that during erysipelas attack, toxins are released continuously and fever may last for 1 to 2 weeks whereas the bacterial toxins were applied as a bolus. For the tumor responses obtained with living streptococci, a plasminogen activator also may have played a role, particularly streptokinase, which is produced by virulent streptococci.¹³¹

It is remarkable that tumor remissions by MBV required continuous and aggressive administration of

bacterial vaccines, eliciting a cascade of cytokines over an extended period of time—days and weeks. The full therapeutic effects achieved with these vaccines may not be reproducible when applying just 1 or 2 recombinant cytokines.¹⁷ Though Coley's cures involved the same immune mediators as modern stand-alone immune therapies, they used all of them in concert over an extended time and in the relevant part of the body.¹²⁰ One should also bear in mind that a century ago, high exposure to tuberculosis was omnipresent and may have substantially contributed to higher effectiveness of the toxins.¹⁷

The question arises whether sarcomas respond better and more dramatically to erysipelas and MBV than carcinomas. They are overrepresented in erysipelas-induced tumor remissions. Mostly sarcomas were treated with MBV, especially soft-tissue sarcoma. Perhaps Coley, being the head of the New York Cancer Hospital's Bone Cancer Department, had greater access to sarcoma patients and was not often consulted by carcinoma patients. His own comments on this issue are inconsistent. There are, in fact, a variety of reports of complete remissions of carcinomas as well, mainly from other physicians.^{24,25,31} Still, the hypothesis was raised that the mesodermal (mesenchymal) embryonic origin of sarcoma tissue might make these tumors more immunogenic.¹⁷

CONCLUSION

Altogether, the responses to fever therapy, spontaneous remissions in the course of infectious diseases, and the observation of the inverse correlation of acute febrile infections and incidence of cancer are remarkable. Still, deciphering the optimal tuning of host response and immune surveillance is far from being solved. A systemic concept is probably needed to understand the orchestrated cytokine and cellular storm resulting in the cures; otherwise, we might forever be left perplexed by the multitude of different kinds of cellular and molecular interactions.¹³²⁻¹³⁴

What is remarkable is that Coley developed the treatment not as we are used to—via "research and development" by the laboratories of biotech industry—but quite differently: through careful clinical observation of hundreds of patients and thorough knowledge of medical and scientific literature combined with critical reflection. Coley was the epitome of a clinician scientist, one of those pioneering individual physicians who made the seminal discoveries, especially in the golden age between 1930 and 1965, that irrevocably changed medicine by bringing us, for instance, sulphonamides, penicillin, cephalosporins, neuroleptics, antidepressants, and steroids.^{135,136} Since then, clinical drug research has moved into the laboratories and the pharmaceutical industry and is presently experiencing an insufficiency crisis.¹³⁷⁻¹³⁹ The strengths of those clinical champions are today remembered and called for again, and so are their virtues. Like Coley, they were proficient in their clinical work, guided by practical scientific thinking, open to the unexpected, and driven by the desire to cure patients.^{135,136,140,141}

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