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REVIEW

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

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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 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

**Figure 1** William Coley, circa 1888, at the start of his medical career.
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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 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]

**Figure 2** Signor Zola, who survived another 8 years after being treated by Coley in 1891.
Reprinted with permission from the Cancer Research Institute.

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 families[16]—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 bone[20]; Hodgkin's lymphoma[21]; osteogenic sarcoma[22,23]; ovarian, uterine, and cervical carcinoma[24]; breast cancer[25]; neuroblastoma[26]; renal cancer[27]; melanoma[28]; testicular cancer[29]; sarcoma of the soft tissues[30]; colorectal cancer[31]; Ewing's sarcoma[32]; and multiple myeloma[33] 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]

| | Median Survival, y | | 10-y Survival Rate | |
|---|---|---|---|---|
| **Tumor type** | **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), influence/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 antitumor- 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-nonself 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-12[119] 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]

**REFERENCES**


1. Hall SS. A commotion in the blood: life, death, and the immune System. New York: Henry Holt and Company; 1997.
2. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases. Am J Med Sci. 1893 May;105(5):487-510.
3. Busch. VI. Verhandlungen ärztlicher Gesellschaften. Berliner Klin Wochenschrift. 1866;3:245-246.
4. Nauts HC. Bacteria and cancer--antagonisms and benefits. Cancer Surv. 1989;8(4):713-23.
5. O'Regan B, Hirshberg C. Spontaneous remission: an annotated bibliography. Sausalito: Institute of Noetic Sciences; 1993.
6. Fehleisen F. Über die Züchtung der Erysipelkokken auf künstlichem Nährboden und ihre Übertragbarkeit auf den Menschen. Dtsch Med Wschr. 1882; 8:553-4.
7. Huth E. Leukämie und Infektion. Kinderärztliche Praxis. 1957;25:448-56.
8. Stephenson HE Jr, Delmez JA, Renden DI, et al. Host immunity and spontaneous regression of cancer evaluated by computerized data reduction study. Surg Gynecol Obstet. 1971 Oct;133(4):649-55.
9. Maurer S, Kölmel KF. Spontaneous regression of malignant melanoma. New York: Cancer Research Institute; 1997.
10. Wiernik PH. Spontaneous regression of lymphoma. 1-14. 1997. Albert Einstein Cancer Center and Montefiore Medical Center. Ref Type: Report.
11. Zygiert Z. Hodgkin's disease: remissions after measles. Lancet. 1971 Mar 20;1(7699):593.
12. Abdelrazeq AS. Spontaneous regression of colorectal cancer: a review of cases from 1900 to 2005. Int J Colorectal Dis. 2007 Jul;22(7):727-36.
13. Nauts HC. The beneficial effects of bacterial infections on host resistance to cancer. End results in 449 cases. 2nd ed. New York: Cancer Research Institute; 1980.
14. Coley WB. Late results of the treatment in inoperable sarcoma by the mixed toxins of erysipelas and bacillus prodigiosus. Am J Med Sci. 1906;131(3):375-430.
15. Nauts HC, Fowler A, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man; a critical analysis of 30 inoperable cases treated by Coley's mixed toxins, in which diagnosis was confirmed by microscopic examination selected for special study. Acta Med Scand Suppl. 1953;276:1-103.
16. Levine DB. The Hospital for the Ruptured and Crippled: William Bradley Coley, third Surgeon-in-Chief 1925-1933. HSS J. 2008 Feb;4(1):1-9.
17. Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. Pharmacol Ther. 1994;64(3):529-64.
18. Pelner L, Fowler A. Host-tumor antagonism. XIII. Sarcoma of the soft tissues treated by bacterial toxins: successful series. J Am Geriatr Soc. 1959 Aug;7(8):624-47.
19. Pelner L, Fowler A. Host-tumor antagonisms. XIV. Sarcoma of the soft tissues treated by bacterial toxins: unsuccessful series. J Am Geriatr Soc. 1959 Sep;7:698-729.
20. Miller TR, Nicholson JT. End results in reticulum cell sarcoma of bone treated by bacterial toxin therapy alone or combined with surgery and/or radiotherapy (47 cases) or with concurrent injection (5 cases). Cancer. 1971 Mar;27(3):524-48.
21. Coley WB. Primary neoplasms of the lymphatic glands including Hodgkin's disease. Ann Surg. 1916 Jan;63(1):35-70.
22. Coley WB, Coley BL. Primary malignant tumors of the long bones: end results in 170 operable cases, including a small group of malignant central sarcoma. Arch Surg. 1926 Dec;13(6):779-836.
23. Nauts HC. Osteogenic sarcoma: End results following immunotherapy with bacterial vaccines 165 cases, or concurrent infections, inflammation or fever, 41 cases. New York: Cancer Research Institute; 1975.
24. Nauts HC. Beneficial effects of acute concurrent infection, inflammation, fever or immunotherapy (bacterial toxins) on ovarian and uterine cancer. New York: Cancer Research Institute; 1977.
25. Nauts HC. Breast cancer: immunological factors affecting incidence, prognosis and survival (Part I-III). New York: Cancer Research Institute; 1984.
26. Fowler GA, Nauts HC. The apparently beneficial effects of concurrent infections, inflammation or fever and of bacterial toxin therapy on neuroblastoma. New York: Cancer Research Institute; 1970.
27. Nauts HC. Enhancement of natural resistance to renal cancer: beneficial effects of concurrent infections and immunotherapy with bacterial vaccines. New York: Cancer Research Institute; 1973.
28. Fowler GA. Enhancement of natural resistance to malignant melanoma with special reference to the beneficial effects of concurrent infections and bacterial toxin therapy. New York: Cancer Research Institute; 1969.
29. Fowler GA. Testicular cancer treated by bacterial toxin therapy as a means of enhancing host resistance. New York: Cancer Research Institute; 1968.
30. Nauts HC. Beneficial effects of immunotherapy (bacterial toxins) on sarcoma of the soft tissues, other than lymphosarcoma. New York: Cancer Research Institute; 1975.
31. Fowler GA. Beneficial effects of acute bacterial infections or bacterial toxin therapy on cancer of the colon or rectum. New York: Cancer Research Institute; 1969.
32. Nauts HC. Ewing's sarcoma of bone: end results following immunotherapy (bacterial toxins) combined with surgery and/or radiation. New York: Cancer Research Institute; 1974.
33. Nauts HC. Multiple myeloma: beneficial effects of acute infections or immunotherapy (bacterial vaccines). New York: Cancer Research Institute; 1975.
34. Coley WB. The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the streptococcus of erysipelas and the bacillus prodigiosus). The Practitioner. 1909; 83:589-613.
35. Coley WB. The treatment of sarcoma with the mixed toxins of erysipelas and bacillus prodigiosus. Boston Med Surg J. 1908;158(6):175-82.
36. Coley WB. The treatment of inoperable sarcoma with the mixed toxins of erysipelas and bacillus prodigiosus. Med Record. 1917;91:965-6.
37. Coley WB. Erysipelas toxins and erysipelas serum in the treatment of inoperable malignant tumors: further observations. Med Record. 1895;47(20):609-12.
38. Johnston BJ. Clinical effect of Coley's toxin. I. A controlled study. Cancer Chemother Rep. 1962 Aug;21:19-41.
39. Johnston BJ, Novales ET. Clinical effect of Coley's toxin. II. A seven-year study. Cancer Chemoth Rep. 1962 Aug;21:43-68.
40. Kölmel KF, Vehmeyer K, Göhring E, Kuhn B, Wieding JU. Treatment of advanced malignant melanoma by a pyrogenic bacterial lysate. a pilot study. Onkologie. 1991;14(5):411-7.
41. Nauts HC. Pyrogen therapy of cancer: a historical overview and current activities. In: National Cancer Institute and American College of Radiology, editor. Proceedings of the International Symposium on Cancer Therapy by Hyperthermia and Radiation, Apr 28-30, 1975:239-50.
42. Chandler JJ, Stark DB, Allen CV, Fletcher WS. Treatment of cancer by bacterial toxins. Am Surg. 1965 Jul;31:443-9.
43. Kempin S, Cirrencione C, Myers J, et al. Combined modality therapy of advanced nodular lymphomas (NL): The role of nonspecific immunotherapy (MBV) as an important determinant of responses and survival. Proc Am Soc Clin Oncol. 1983;24:56.
44. Kempin S, Cirrincione C, Straus DS, et al. Improved remission rate and duration in Nodular Non-Hodgkin Lymphoma (NNHL) with the use of mixed bacterial vaccine (MBV). Proc Am Assoc Cancer Res. 1981;22:514.
45. Oettgen HF, Old LJ, Hoffmann MK, Moore MA. Antitumor effects of endotoxin: possible mechanisms of action. In: Homma JY, editor. Bacterial endotoxin: chemical, biological and clinical aspects. Weinheim: Verlag Chemie; 1984. p. 205-22.
46. Tang ZY, Zhou HY, Zhao G, et al. Preliminary result of mixed bacterial vaccine as adjuvant treatment of hepatocellular carcinoma. Med Oncol Tumor Pharmacother. 1991;8(1):23-8.
47. Axelrod RS, Havas HF, Murasko DM, Bushnell B, Guan CF. Effect of the mixed bacterial vaccine on the immune response of patients with non-small cell lung cancer and refractory malignancies. Cancer. 1988 Jun 1;61(11):2219-30.
48. Havas HF, Axelrod RS, Burns MM, Murasko DM, Goonewardene M. Clinical results and immunologic effects of a mixed bacterial vaccine in cancer patients. Med Oncol Tumor Pharmacother. 1993;10(4):145-58.
49. Richardson MA, Ramirez T, Russell NC, Moye LA. Coley toxins immunotherapy: a retrospective review. Altern Ther Health Med. 1999 May;5(3):42-7.
50. Hoption Cann SA, van Netten JP, Van Netten C. Acute infections as a means of cancer prevention: opposing effects to chronic infections? Cancer Detect Prev. 2006;30(1):83-93.
51. Schmidt R. Krebs und Infektionskrankheiten. Med Klin. 1910;(43):1690-3.
52. Engel P. Über den Infektionsindex der Krebskrankheiten. Wien Klin Wochenschr. 1934;(37):1118-9.
53. Sinek F. Versuch einer statistischen Erfassung endogener Faktoren bei Carcinomkranken. Z Krebsforsch. 1936;44:492-527.
54. Güttich H. [Are tonsillectomized patients less subject to carcinoma of the upper respiratory and gastrointestinal tract?] HNO. 1960 Nov;9:47-9. German
55. Matzker J, Schmidt P. [On the problem of the relation between the tonsils and carcinoma of the respiratory and digestive tracts]. Z Laryngol Rhinol Otol. 1963 May;42:363-71. German.
56. West RO. Epidemiologic study of malignancies of the ovaries. Cancer. 1966 Jul;19(7):1001-7.
57. Wynder EL, Dodo H, Barber HR. Epidemiology of cancer of the ovary. Cancer. 1969 Feb;22(2):352-70.
58. Denk W, Karber K. [Studies on the possibility of immunoprophylaxis of carcinoma]. Österr Z Erforsch Bekampf Krebskr. 1970;25(1):30-9. German.
59. Witzel L. [History and other diseases in patients with malignant neoplasms]. Med Klin. 1970 May;65(18):876-9. German.
60. Joly DJ, Lilienfeld AM, Diamond EL, Bross ID. An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. Am J Epidemiol. 1974 Mar;99(3):190-209.
61. Matzker J, Klasen HP. Tonsillektomie und Leukämie im Kindesalter. Laryngol Rhinol Otol (Stuttg). 1975;54(12):991-7.
62. Matzker J, Steinberg A. [Tonsillectomy and leukemia in adults (author's transl)]. Laryng Rhinol Otol (Stuttg). 1976 Sep;55(9):721-5. German.
63. Newhouse ML, Pearson RM, Fullerton JM, Boesen EAM, Shannon HS. A case control study of carcinoma of the ovary. Br J Prev Soc Med. 1977 Sep;31(3):148-53.
64. Jentgens H, Matzker J, Steinhaus C. [Frequency of tonsillectomy in bronchial cancer patients (author's transl)]. Laryng Rhinol Otol (Stuttg). 1978 Mar;57(3):190-3. German.
65. McGowan L, Parent L, Lednar W, Norris HJ. The woman at risk for developing ovarian cancer. Gynecol Oncol. 1979 Jun;7(3):325-4.
66. Grufferman S, Wang HH, DeLong ER, Kimm SYS, Delzell ES, Falletta JM. Environmental factors in the etiology of rhabdomyosarcoma in childhood. J Natl Cancer Inst. 1982 Jan;68(1):107-13.
67. Remy W, Hammerschmid K, Zänker KS et al. Tumorträger haben selten Infekte in der Anamnese. Med Klin. 1983;78(3):95-8.
68. Ronne T. Measles virus infection without rash in childhood is related to disease in adult life. Lancet. 1985 Jan 5;1(8419):1-5.
69. van Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and infectious diseases in the first year of life: a register-based case-control study. Am J Epidemiol. 1986 Oct;124(4):590-4.
70. Chilvers C, Johnson B, Leach S, Taylor C, Vigar E. The common cold, allergy and cancer. Br J Cancer. 1986 Jul;54(1):123-6.
71. Grossarth-Maticek R, Frentzel-Beyme R, Kanazir D, Jankovic M, Vetter H. Reported herpes-virus-infection, fever and cancer incidence in a prospective study. J Chronic Dis. 1987;40(10):967-76.

72. Abel U, Becker N, Angerer R, et al. Common infections in the history of cancer patients and controls. J Cancer Res Clin Oncol. 1991;(117):339-44.
73. Kölmel KF, Gefeller O, Haferkamp B. Febrile infections and malignant melanoma: results of a case-control study. Melanoma Res. 1992 Sep;2(3):207-11.
74. Wrensch M, Weinberg A, Wiencke J, et al. Does prior infection with varicella-zoster virus influence risk of adult glioma? Am J Epidemiol. 1997 Apr 1;145(7):594-7.
75. Albonico HU, Bräker HU, Hüsler J. Febrile infectious childhood diseases in the history of cancer patients and matched controls. Med Hypotheses. 1998 Oct;51(4):315-20.
76. Mastrangelo G, Fadda E, Milan G. Cancer increased after a reduction of infections in the first half of this century in Italy: etiologic and preventive implications. Eur J Epidemiol. 1998 Dec;14(8):749-54.
77. Kölmel KF, Pfahlberg A, Mastrangelo G, et al. Infections and melanoma risk: results of a multicentre EORTC case-control study. Melanoma Res. 1999 Oct;9(5):511-9.
78. Schlehofer B, Blettner M, Preston-Martin S, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer. 1999 Jul 19;82(2):155-60.
79. Hoffmann C, Rosenberger A, Troger W, Buhring M. [Childhood diseases, infectious diseases, and fever as potential risk factors for cancer?] Forsch Komplementarmed Klass Naturheilkd. 2002 Dec;9(6):324-30; discussion 323. German.
80. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. Am J Epidemiol. 2004 May 1;159(9):843-51.
81. Roman E, Simpson J, Ansell P, et al. Childhood acute lymphoblastic leukemia and infections in the first year of life: a report from the United Kingdom Childhood Cancer Study. Am J Epidemiol. 2007 Mar 1;165(5):496-504.
82. Cardwell CR, McKinney PA, Patterson CC, Murray LJ. Infections in early life and childhood leukaemia risk: a UK case-control study of general practitioner records. Br J Cancer. 2008 Nov 4;99(9):1529-33.
83. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault GP. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. Am J Epidemiol. 2008 Mar 1;167(5):598-606.
84. Wrotek S, Kamecki K, Kwiatkowski S, Kozak W. Cancer patients report a history of fewer fevers during infections than healthy controls. J Preclin Clin Res. 2009;3(1):031-5.
85. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. Int J Epidemiol. 2010 Jun;39(3):718-32.
86. Rudant J, Orsi L, Menegaux F, et al. Childhood acute leukemia, early common infections, and allergy: the ESCALE Study. Am J Epidemiol. 2010 Nov 1;172(9):1015-27.
87. Vestergaard H, Westergaard T, Wohlfahrt J, Hjalgrim H, Melbye M. Tonsillitis, tonsillectomy and Hodgkin's lymphoma. Int J Cancer. 2010 Aug 1;127(3):633-7.
88. Urayama KY, Ma X, Selvin S, et al. Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. Int J Cancer. 2011 Apr 1;128(7):1632-43.
89. Cramer DW, Finn OJ. Epidemiologic perspective on immune-surveillance in cancer. Curr Opin Immunol. 2011 Apr;23(2):265-71.
90. Takita H. Effect of postoperative empyema on survival of patients with bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1970 May;59(5):642-4.
91. LeRoux BT. Empyema thoracis. Br J Surg. 1965 Feb;52:89-99.
92. Sensenig DM, Rossi NP, Ehrenhaft JL. Results of the surgical treatment of bronchogenic carcinoma. Surg Gynecol Obstet. 1963 Mar;116:279-84.
93. Ruckdeschel JC, Codish SD, Stranaham A, McKneally MF. Postoperative empyema improves survival in lung cancer. Documentation and analysis of a natural experiment. N Engl J Med. 1972 Nov 16;287(20):1013-7.
94. McKneally MF, Maver C, Kausel HW. Regional immunotherapy of lung cancer with intrapleural B. C. G. Lancet. 1976 Feb 21;1(7956):377-9.
95. Cady B, Cliffton EE. Empyema and survival following surgery for bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1967 Jan;53(1):102-8.
96. Minasian H, Lewis CT, Evans SJ. Influence of postoperative empyema on survival after pulmonary resection for bronchogenic carcinoma. Br Med J. 1978 Nov 11;2(6148):1329-31.
97. Brohee D, Vanderhoeft P, Smets P. Lung cancer and postoperative empyema. Eur J Cancer. 1977 Dec;13(12):1429-36.
98. Müller W, Regazzoni P. [Does a local postoperative infection improve the prognosis in colonic carcinoma?] Helv Chir Acta. 1975 Mar;42(1-2):205-8. German.
99. Fucini C, Bandettini L, D'Elia M, Filipponi F, Herd-Smith A. Are postoperative fever and/or septic complications prognostic factors in colorectal cancer resected for cure? Dis Colon Rectum. 1985 Feb;28(2):94-5.
100. Nowacki MP, Szymendera JJ. The strongest prognostic factors in colorectal carcinoma. Surgicopathologic stage of disease and postoperative fever. Dis Colon Rectum. 1983 Apr;26(4):263-8.
101. Papachristou DN, Fortner JG. Effect of postoperative wound infection on the course of stage II melanoma. Cancer. 1979 Mar;43(3):1106-11.
102. Jeys LM, Grimer RJ, Carter SR, Tillman RM, Abudu A. Post operative infection and increased survival in osteosarcoma patients: are they associated? Ann Surg Oncol. 2007 Oct;14(10):2887-95.
103. Teucher G, Schindler AE. [Postoperative fever and prognosis in breast cancer]. Arch Geschwulstforsch. 1987;57(4):309-17. German.
104. Jackson RM, Rice DH. Wound infections and recurrence in head and neck cancer. Otolaryngol Head Neck Surg. 1990 Apr;102(4):331-3.
105. Grandis JR, Snyderman CH, Johnson JT, Yu VL, D'Amico F. Postoperative wound infections. A poor prognostic sign for patients with head and neck cancer. Cancer. 1992 Oct 15;70(8):2166-70.
106. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99.
107. Boyle P, Levin B, International Agency for Research on Cancer. World cancer report 2008. Lyon: International Agency for Research on Cancer; 2008.
108. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002 Dec 19-26;420(6917):860-7.
109. Ryan SO, Gantt KR, Finn OJ. Tumor antigen-based immunotherapy and immunoprevention of cancer. Int Arch Allergy Immunol. 2007;142(3):179-89.
110. Sporn MB, Roberts AB. Peptide growth factors are multifunctional. Nature. 1988 Mar 17;332(6161):217-9.
111. Nathan C, Sporn MB. Cytokines in context. J Cell Biol. 1991 Jun;113(5):981-6.
112. Silverstein AM. A history of immunology. San Diego, New York, Boston, London, Sydney, Tokyo, Toronto: Academic Press; 1989.
113. Hewitt HB. Animal tumor models and their relevance to human tumor immunology. J Biol Response Modif. 1982;1(2):107-19.
114. Nossal GJ. The case history of Mr. T.I. Terminal patient or still curable? Immunol Today. 1980 Jul;1(1):5-9.
115. Hewitt HB, Blake ER, Walder AS. A critique of the evidence for active host defence against cancer, based on personal studies of 27 murine tumours of spontaneus origin. Br J Cancer. 1976 Mar;33(3):241-59.
116. Shear MJ, Turner FC, Perrault A, Shovelton T. Chemical treatment of tumors. V. Isolation of the hemorrhage-producing fraction from Serratia marcescens (Bacillus prodigiosus) culture filtrate. J Natl Cancer Inst. 1943;4:81-97.
117. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A. 1975 Sep;72(9):3666-70.
118. Old LJ. Tumor necrosis factor (TNF). Science. 1985 Nov 8;230(4726):630-2.
119. Tsung K, Norton JA. Lessons from Coley's toxin. Surg Oncol. 2006 Jul;15(1):25-8.
120. Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev. 2009 Aug;20(4):271-81.
121. Finn OJ. Cancer immunology. N Engl J Med. 2008 Jun 19;358(25):2704-15.
122. Matzinger P. The danger model: a renewed sense of self. Science. 2002 Apr 12;296(5566):301-5.
123. Hobohm U. Fever and cancer in perspective. Cancer Immunol Immunother. 2001 Oct;50(8):391-6.
124. Baronzio G, Gramaglia A, Fiorentini G. Hyperthermia and immunity. A brief overview. In Vivo. 2006 Nov-Dec;20(6A):689-95.
125. Fisher DT, Vardam TD, Muhitch JB, Evans SS. Fine-tuning immune surveillance by fever-range thermal stress. Immunol Res. 2010 Mar;46(1-3):177-88.
126. Hasday JD, Singh IS. Fever and the heat shock response: distinct, partially overlapping processes. Cell Stress Chaperones. 2000 Nov;5(5):471-80.
127. Skitzki JJ, Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. Curr Opin Investig Drugs. 2009 Jun;10(6):550-8.
128. Roti Roti JL. Cellular responses to hyperthermia (40-46 degrees C): Cell killing and molecular events. Int J Hyperthermia. 2008 Feb;24(1):3-15.
129. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002 Aug;3(8):487-97.
130. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol. 2010 Jun;11(6):561-70.
131. Zacharski LR, Sukhatme VP. Coley's toxin revisited: immunotherapy or plasminogen activator therapy of cancer? J Thromb Haemost. 2005 Mar;3(3):424-7.
132. Bonn D. Biocomplexity: look at the whole, not the parts. Lancet. 2001 Jan 27;357(9252):288.
133. Orosz CG. An introduction to immuno-ecology and immuno-informatics. In: Segel LA, Cohen IR, editors. Design principles for the immune system and other distributed autonomous systems. Oxford, New York: Oxford University Press; 2001. p. 125-49.
134. Kienle GS, Kiene H. "Beyond reductionism"—zur Notwendigkeit komplexer, organismischer Ansätze in der Tumorimmunologie und Onkologie. In: Kienle GS, Kiene H, editors. Die Mistel in der Onkologie. Fakten und konzeptionelle Grundlagen. Stuttgart, New York: Schattauer Verlag; 2003:333-432.
135. Horrobin DF. Effective clinical innovation: an ethical imperative. Lancet. 2002 May 25;359(9320):1857-8.
136. Horrobin DF. Are large clinical trials in rapidly lethal diseases usually unethical? Lancet. 2003 Feb 22;361(9358):695-7.
137. Horrobin DF. Innovation in the pharmaceutical industry. J R Soc Med. 2000 Jul;93(7):341-5.
138. Drews J. In quest of tomorrow's medicines. Berlin, Heidelberg, New York: Springer; 2003.
139. Angell M. The truth about drug companies. New York: Random House; 2004.
140. Shaywitz DA, Ausiello DA. Preserving creativity in medicine. PLoS Med. 2004 Dec;1(3):e34.
141. Kienle GS, Kiene H. Clinical judgement and the medical profession. J Eval Clin Pract. 2011 Aug;17(4):621-7.