(/)

Healing Heat: Harnessing Infection to Fight Cancer

BY UWE HOBOHM (/AUTHOR/UWE_HOBOHM)

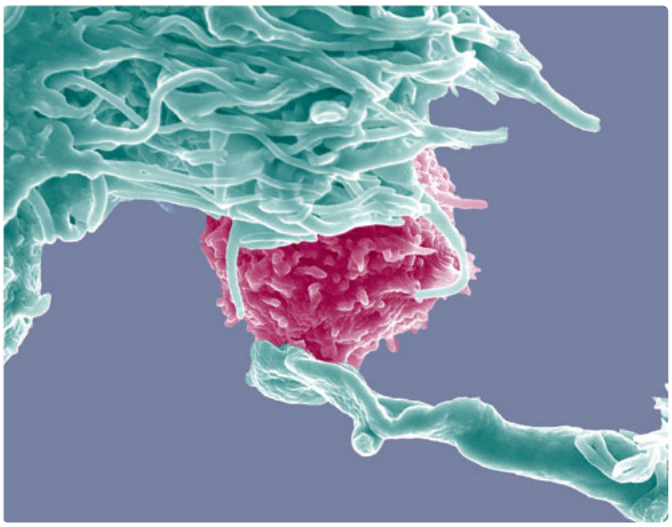
Modern immunology plus historic experiments suggest a better way to gear up the human immune system to battle malignant disease

BIOLOGY (HTTPS://WWW.AMERICANSCIENTIST.ORG/TOPICS-NAMES/BIOLOGY) • MEDICINE (HTTPS://WWW.AMERICANSCIENTIST.ORG/TOPICS-NAMES/MEDICINE) • IMMUNOLOGY (HTTPS://WWW.AMERICANSCIENTIST.ORG/FREE-TAG-NAMES/IMMUNOLOGY)

THIS ARTICLE FROM ISSUE
JANUARY–FEBRUARY 2009
VOLUME 97, NUMBER 1
PAGE 34
DOI: 10.1511/2009.76.34
(HTTPS://DOI.ORG/10.1511/20

Conventional wisdom long held that the human immune system was no match for cancer. Born of native cells, the logic went, cancer fooled the immune system into concluding it was harmless. Thus protected from attack, cancer easily thrived until its host died.

(/)



Olivier Schwartz, Institute Pasteur/Science Photo Library, Nature Cell

A deeper understanding of our biological defenses has changed that. The human immune system does battle cancer. But we could better optimize our defenses to fend off malignant disease. That's clear from cancer treatments attempted in New York City and Germany as early as the 19th century. Those experiments and other undervalued evidence from the medical literature suggest that acute infection—in contrast to chronic infection, which sometimes causes cancer—can help a body fight tumors.

(/)

It's not the pathogens that do the good work. But the way our bodies respond to the pathogens is key. Infection events, especially those that produce fever, appear to shift the innate human immune system into higher gear. That ultimately improves the performance of crucial biological machinery in the adaptive immune system. This lesson comes, partly, from doctors who risked making patients sicker to try to make them better.

Toxin Therapy

Elisabeth Dashiell was 17 years old when she entered New York Hospital in the autumn of 1890 with severe pain in her hand but no sign of infection. Her newly trained surgeon, William B. Coley, saw no improvement after a period of observation. In November 1890, a biopsy revealed round-cell sarcoma, a relatively rare form of cancer originating in soft tissue and bone.

Photograph courtesy of the Cancer Research Institute.

Shortly after the biopsy, Dashiell's arm was amputated below her elbow, but her cancer still spread ferociously. In December a tumor was detected in her right breast; within days, nodules appeared in her left breast. By January a huge tumor swelled in her abdomen and her heart began to fail. On January 23, 1891, Dashiell died.

Medicine back then offered little more than amputation and morphine to cancer patients such as Dashiell. Shocked by his ineffectiveness, Coley dove into hospital records and the medical literature for clues to how to help more. He found about 90 sarcoma case reports. About half contained follow-up histories. The one that grabbed him most involved Fred Stein.

(/)

Stein, a German immigrant, had been diagnosed with cheek sarcoma in 1884. Despite four operations, his cancer kept recurring. He was considered a hopeless case. However, in late 1884 Stein developed high fever from erysipelas, a postoperative skin disease common in that era. To the great surprise of his physicians, his tumor disappeared. Stein was discharged from the hospital in February 1885.

Five months after Elisabeth Dashiell died, Coley tracked Stein to New York City's Lower East Side. Photographed and examined, Stein showed no trace of residual cancer six years after his puzzling recovery. That drove Coley to dig deeper for records of similar cases. The young doctor, who had studied some German at Yale University, likely encountered a report published more than two decades earlier, in 1868, in the journal *Berliner Klinische Wochenschrift*.

The German physician W. Busch reported that he had observed a patient's tumor "re-absorbed" after a high fever. Unconstrained by modern ethics rules, Busch tested for some connection himself. That summer, by coincidence, a patient with a mild erysipelas infection that followed an injury and a 19-year-old girl with a huge sarcoma of the neck entered Busch's clinic at around the same time. Over five months, the sarcoma had grown to the size of a child's head. The young woman's breathing was threatened; she could not completely close one eye.

Before antibiotics, erysipelas was one of the leading causes of death from postoperative infections in hospitals. Still, Busch burned a small piece of skin over the girl's tumor and attached a cotton pad taken from the erysipelas patient onto her wound. The surrounding skin developed signs of erysipelas and the patient developed a high fever—104 degrees Fahrenheit. Her tumor, which had been tight and dense, softened and shrank rapidly. Within two weeks it reached the size of a small apple. She could close her eyes and breathe freely. Unfortunately, the young lady developed circulatory problems, and steps had to be taken to strengthen her weak condition. With the disappearance of the skin inflammation, the tumor reached its prior size. How she fared after leaving the clinic is not known.

In his literature search, Coley found more than 40 cases of disappearance of malignancies during an erysipelas attack. He came across another medical pioneer, Friedrich Fehleisen, also in Germany, who was the first to use cultured bacteria in related experiments. After successes and failures, Fehleisen discontinued the work. Still, Coley decided to try for himself.

(/)

Photo courtesy of the Cancer Research Institute.

In April 1891 an Italian immigrant, Mr. Zola, presented at New York Hospital with a large sarcoma tumor in his neck and an egg-sized metastasis in his right tonsil. He had been operated on twice before but was in hopeless condition. He could hardly speak or swallow and was unable to eat solid food. His life expectancy was, at the very most, a few months. He had nothing to lose by undergoing an experimental treatment.

Since erysipelas was so hazardous, the hospital was reluctant to host Coley's experiment, so it was performed in a private apartment. Colleagues at the College of Physicians and Surgeons, now part of Columbia University, prepared the bacteria. Three applications were delivered over three weeks, with minor success. Zola's temperature rose only slightly, and he showed no sign of full-blown infection. Coley tried a fresh preparation and a larger dose. Within hours, Zola developed severe chills, headache and vomiting. His temperature did not reach what one could expect from a full-blown erysipelas infection; it did not exceed 102 degrees Fahrenheit. Both tumors diminished in size. About one month after the treatment began, Zola could eat again.

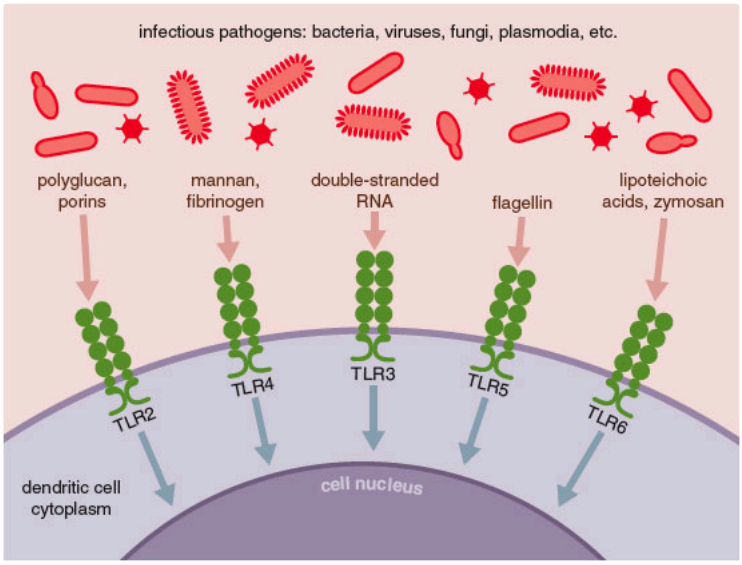
Via a friend, Coley obtained fresh and potent bacteria culture from the leading German bacteriologist, Robert Koch. That fall, he again treated Zola, whose temperature that time rose above 104 degrees, with nausea, vomiting and severe pain. The infection almost killed him, but within two weeks, the neck tumor was not observable. The tonsil tumor stopped growing. Zola was in excellent health when Coley saw him four years later.

(/)

During the following two years Coley attempted to infect 12 patients who had inoperable cancer. He failed to induce a full-blown infection in four and succeeded in eight. All eight responded. Six had partial tumor remissions. Two showed full remission. But two patients died from infection. So Coley abandoned living cultures and turned toward what today we would call a bacterial extract.

Refining a Method

Coley tried inactivated microbes on four patients but obtained only modest fever-inducing effects and temporary changes in their tumors. The preparations likely were too weak. By the end of 1892, the French doctor G. H. Roger had published his observation that the virulence of the erysipelas bacterium, *Streptococcus pyogenes,* increased when it was grown in the presence of another, then called *Bacillus prodigiosus*, now *Serratia marcescens*, a mild pathogen involved in eye and urinary infections.



Barbara Aulicino

In January 1893 Coley administered for the first time one variant of what today are still called “Coley’s toxins.” It was a heat-sterilized, combined culture *of S. pyogenes* and *S. marcescens* bacteria administered by injection. The patient was a 16-year-old boy with a large inoperable abdominal tumor, a malignant sarcoma. After receiving increasing doses over 10 weeks, the boy developed symptoms mimicking those of a heavy erysipelas infection: chills, headache, fever, local redness and swelling at injection sites. The tumor shrank by 80 percent. Coley kept in touch with his patient, who remained cancer-free for more than 20 years.

(/)

Coley treated another five patients during 1893. No result was as promising as his first. Coley published the results of his experiments in the *The American Journal of the Medical Sciences* under the title "The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases" in 1893. The report stirred considerable excitement—for a while.

At the beginning of the 20th century radiation treatment came on the cancer therapy scene. This new procedure captured nearly the full attention of the oncology community due to its immediately visible effects. One could now, it seemed, x ray away tumors. Within the medical mainstream, interest in Coley's methods faded.

Still, some physicians did try to test Coley's treatment. Nicholas Senn of Rush Medical College in Chicago reported uniform failure of the method. William Keen, a surgeon in Philadelphia, failed to obtain a response in seven patients. A Dr. Caulkins of Watertown, New York, reported a large number of successes, as did Dr. Matagne from Belgium, who prepared his own fresh extracts. Matagne published his observations in lower-tier French and Belgian journals.

Two stubborn surgeons, S. L. Christian and L. A. Palmer, at the U.S. Marine Hospital in Stapleton, New York, reported a spectacular cure in 1928. Two years before, a U.S. Marine captain they described as "G. B." developed bone sarcoma and endured an above-the-knee amputation. He was 31 years old. In 1926, G. B. received daily injections of "Coley's fluid" from January 5 to February 20, until he seemed too weak to endure more. Treatments were started and stopped that spring and started again that summer, fall and winter, with daily injections totaling 20 weeks cumulatively. The patient was last examined on January 9, 1928. No evidence of disease was present.

Coley, throughout his 40-plus-year career, treated hundreds with multiple versions of his toxin. He never achieved a clear-cut, uniform result. Some patients responded. Among them, some were cured, but some were not. At a 1934 meeting, Coley discussed 44 cases of Ewing's sarcoma. Twelve out of 44 patients had been treated with radiation by other physicians and none of these survived five years. But the remaining 32 patients had been treated with bacterial extract by Coley. Twelve of them remained disease free for more than five years. A five-year survival rate of zero after radiation and 38 percent after Coley's treatments merited deeper scrutiny.

Helen Coley Nauts, Coley's daughter, meticulously reexamined her father's clinical cases after his death. This was not easy. Undoubtedly a man of determination, Coley was not a methodical scientist. His patient records were a mess, he treated different patients for different time periods and his bacterial extracts, over time, were inconsistently made. Coley Nauts counted 15 different preparations. Eleven of them, she concluded, were not potent enough to have a strong effect.

(/)

Coley Nauts determined that her father had treated several hundred patients by the time he died in 1936, many of whom had received radiation and sometimes surgery as well. To estimate the overall success of extracts, the analysis should be restricted to patients with inoperable cancer and treated by toxin alone. In another review from 1994, immunologist and oncology researcher Charles Starnes identified 170 such patients with adequate medical records (121 with some form of sarcoma, 43 with carcinoma and myeloma, and 6 with melanoma). The remission rate among them was 64 percent; the five-year survival rate was more than 44 percent.

According to the analyses of Coley Nauts and Starnes, treatment success correlated with length of therapy and the fevers induced by the toxins. Higher was better. This correlation was reported among several other observations but without emphasis or any explanation by the authors.

Only a few uncoordinated attempts to apply Coley's ideas were pursued from mid-century on. Bacterial extracts used in the later studies, in the 1960s and 1970s, were commercial preparations called MBV (produced by Bayer) and Vaccineurin (produced by Südmedica of Munich). They were similar to, but not identical to, Coley's extracts. The experimenters appeared to be hunting for anticancerous substances that could be applied a limited number of times to be effective, a traditional cancer therapy model embraced by pharmaceutical companies. Length of treatment and fever level were not adequately considered. A majority of the patients in the studies had been pretreated with chemotherapy, radiation therapy or both, measures that likely distorted the immune response that appears to be triggered by the bacterial extracts. Results were mixed: several remissions, even long-lasting ones, with several failures.

Well-controlled studies of bacterial-extract cancer treatment that incorporate all the lessons from the retrospective analysis of Coley's and other treatments have not been pursued since. But medical case studies, cancer epidemiology and our more precise understanding of immunology make a strong case that they should.

Spontaneous regression or remission is the partial or complete disappearance of an untreated malignant tumor or a tumor treated with a therapy considered inadequate to exert significant influence. It sounds like fantasy, but about 1,000 case studies in the medical literature during the past century detail spontaneous regression from cancer. Surely more have occurred. And there's a pattern to some of the cases.

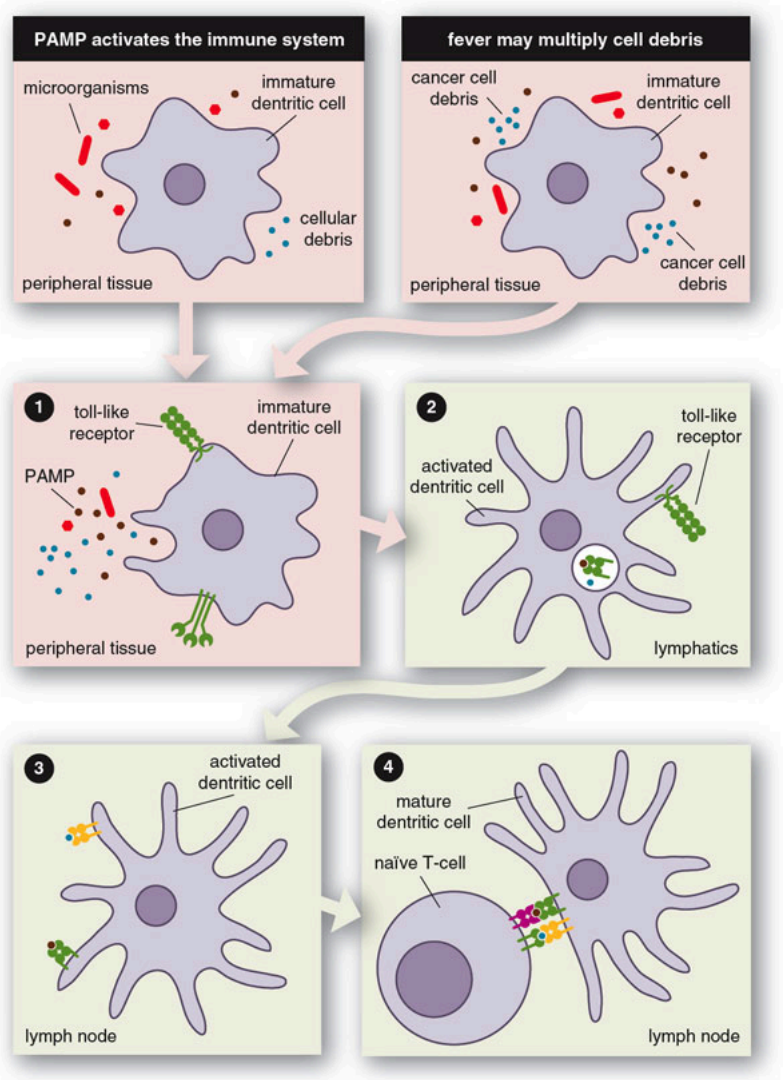
A prior fever was recorded in 25 to 80 percent of documented cases of spontaneous regression of cancer. For instance, Diamond and Luhby in 1951 reported 26 spontaneous remissions in a cohort of 300 cases of childhood leukemia; 80 percent were accompanied by infection. Stephenson and

(/)

colleagues in 1971 investigated 224 cases of spontaneous regression and reported that in 62 cases, or 28 percent, regression was preceded by either an infection or a persistent temperature elevation. In many cases, *S. pyogenes*, the pathogen that produced erysipelas, was involved.

Harnessing Immunity

It is not true, as Coley believed of *S. pyogenes*, that all these pathogens produce some cagey anti-cancerous substance. Even malaria was reported in the case histories—a disease caused by plasmodia rather than a virus or bacterium. It's unlikely that pathogens of such disparate evolutionary roots could produce the same cancer fighter. Much more likely is that the sequence of immune reactions triggered by the infections was the same.



Barbara Aulicino

(/)

The immune system is capable of finding a malignant cell, just as it is able to localize a bacterium, a virus, a worm or a malaria plasmodium. As early as 1956, scientists observed that the survival rates of gastric cancer patients correlated with the number of a specific type of immune cell observed in and around their tumors. The more tumor infiltrating lymphocytes (TIL), the better. Still, millions of people die from cancer each year. Why?

Barriers must exist to prevent an organism's immune system from attacking its own tissue. Otherwise, devastating autoimmune diseases would be more common. Mammalian immune systems are structured to maintain a delicate balance between recognition and removal of pathogens and not attacking "self." Bacteria and viruses are invaders that the immune system generally is poised to attack. Malignant cells, derived from native cells, don't generate the same reaction since they are "self"—at least that was the long held explanation.

Cancer cells can carry hundreds of mutations that distinguish them from healthy cells. But the immune system often remains in an "observer" state in their presence rather than engaging in battle as it does against bacterial or viral infections. The reason for this incomplete immune response is a long-standing puzzle in cancer immunology. William Coley's experiments may help today's scientists solve it.

The human immune system can be broadly divided into two parts, the innate and the adaptive. The older, innate immune system reacts within minutes after invading pathogens are encountered. The adaptive system, which employs evolutionarily younger and more customized tools, takes longer to generate specialized antibodies and T cells to attack threats.

A look into vaccinology illustrates why involvement of the innate system may be crucial. Ordinary vaccines such as those against measles, smallpox, tuberculosis or whooping cough either contain "attenuated" live pathogens, sterilized pathogens or pathogenic antigens. These components are geared toward the adaptive immune system; they lead to the production of pathogen-specific antibodies or T cells.

But all vaccines contain another component, so-called adjuvants. For decades nobody understood why adjuvants enhance the immune reaction. The immunologist Charles Janeway called adjuvants "doctors' dirty little secret." Today we know that adjuvants stimulate the underestimated portion of the immune system, the innate arm. Some vaccines would be almost useless without an adjuvant.

Evolution wired both arms of our immune response to work together. A defective innate system allows pathogens to attack more rapidly, putting the slower adaptive system at risk of being overrun. For too long, the attention in cancer immunology was focused on the adaptive part of the immune system

(/)

alone. Only in recent years have cancer immunologists turned their attention to understanding the role of the innate system.

Scientists have expanded the observation from the 1950s that a high number of lymphocytes near gastric tumor tissue improves patient survival. The same pattern has been found in more than 3,400 patients with cancer of the breast, bladder, colon, prostate, ovary, rectum and brain. In the case of breast cancer, the difference was striking. Patients with high numbers of TIL had a six-year survival rate of more than 60 percent, whereas no patients with very low numbers survived. P. H. Cugnenc *et al.* observed in 2006 that the location and density of T cells within colorectal tumors is a better predictor of patient survival than tumor classification by size and spread. This is a profound observation, since it proves that the immune system can constrain cancer, at least for a while.

In these cases, presumably, constant elimination of some malignant tissue takes place, although not complete eradication. At the same time tumor cells evolve due to their inherent genetic instability. They produce variants leading to successive cell populations with different immunogenicity—different vulnerability. Thus, while one variant cell is detected and destroyed, another variant develops for which the immune system has to generate novel bullets. The outcome is often fatal.

Dendritic cells, which link the innate and adaptive immune systems, likely are hugely important players in restraining cancer. Dendritic cells act like patrolling sentries, prowling boundaries between the body and the outer world on and under skin, within the epidermis and within mucous membranes in the mouth, nose, ear and colon. These cells ingest pathogens and cell debris and produce from them structures known as antigens—biological fingerprints that stimulate T cells and B cells to customize their immune attacks. Dendritic cells carry those antigens to lymph nodes and display them on their surfaces to T cells, key actors in the molecular chain that launches adaptive immune attacks.

There is one important requirement in this scenario that has not been recognized until recently. Dendritic cells need so-called danger signals to become maximally activated. Cancer cells do not produce the right signals to activate them; but certain classes of bacterial and viral components do. They are called pathogen-associated molecular patterns (PAMP).

PAMP is the name for a collection of chemically diverse substances found in parts of biological invaders such as the lipopolysaccaride in bacterial cell walls or the flagellin in bacterial propellers. PAMP also includes double-stranded RNA found in viruses and parts of infectious fungi, such as mannan or zymosan. They bind to the same protein family in the human body as do adjuvants in

(/)

vaccines: so-called Toll-like receptors (TLR*),* which dendritic cells employ. No other class of substances is known to induce maturation of dendritic cells as efficiently as PAMP. That ability may explain how bacterial infection, in the presence of fever, can mobilize immune attacks against cancer.

The details of this hypothesized cross-immune stimulation are not yet known. But a hint may be distilled from an experiment published in 2004. Cancers are known to tone down immune responses. They produce and release immune-suppressing signals into their environment, phenomena called tumor escape or tumor tolerance induction. Drew Pardoll at Johns Hopkins University and colleagues wanted to break this tolerance and revitalize a normal immune response against an established tumor in mice. His group administered dendritic cells plus tumor antigen, but tolerance for the antigen remained.

In a second experiment, dendritic cells were infected with a virus. That time, tolerance for the cancer antigen was broken and the immune system, pushed into a higher gear, launched a full attack. This makes sense. Viruses produce PAMP. Dendritic cells are fully activated with help from PAMP.

This suggests an explanation for Coley's success with some of his patients and for those documented spontaneous cancer remissions after fevers. Dendritic cells ingest both pathogens and dying cells and eventually display antigens needed to activate T cells, probably by displaying both on their surface. And it's likely that fever has an important role in this scenario. As Klemens Trieb and colleagues reported back in 1994, cancer cells can be more vulnerable to heat than normal cells. Fever produces heat, so it is fair to argue that fever may produce an unusually high amount of cell debris from cancer cells, possibly resulting in potentially more cancer-cell antigens being collected by dendritic cells. The immune system requires a certain amount of antigen for full activation; low antigen levels are ignored.

Fever As Weapon

But fever is not recognized as a therapeutic tool in clinical settings. In fact, fever is a nuisance to patients and staff. Fever accompanies dangerous infections, so its removal is equated with removing danger. A proliferative infection can cause circulatory problems, and patients experiencing them need to be monitored closely. Multiple incentives persist to use an aspirin or another antipyretic to shut fever down.

But fever induced by sterilized pathogens or pathogenic substances is much less dangerous than a proliferative infection. Circulatory problems caused by Vaccineurin, a fever-inducing drug containing *Streptococcus* extracts used in German private clinics until the early 1990s, were extremely rare. These

(/)

fevers usually lasted less than a day and then declined automatically.

SIDEBAR

What The Literature Says

Within the immense, international cancer literature, multiple publications observe that infections appear to be associated with lower cancer risk later in life and to increase the odds of cancer regression. This observation does not hold for chronic infections, which can actually induce cancers. Only six of the more recent studies included age-adjusted controls.

Some clinical tests using PAMP have been pursued in recent years. That comes from the recognition that PAMP represents a novel group of substances that could be patented for profit. However, experiments involving PAMP have been guided by magic-bullet thinking favored by pharmaceutical companies. Important lessons from Coley and his contemporaries, including those related to fever, are not being adequately incorporated in the testing. Fever usually is suppressed as an adverse reaction during the tests. But that is not all.

PAMP therapies usually are tested in patients who have had prior chemotherapy, radiation therapy or both. These patients have compromised immune systems. Optimal results can only be expected in patients with noncompromised immune systems. Also, in contrast to a natural infection, where a mixture of PAMP molecules invades a host, only single substances are tested in the clinical trials. That's the case even though vaccine research has taught us that living attenuated or sterilized pathogens induce a much stronger immune response than single antigens. Single PAMP, in general, will induce a much weaker immune response than would bacterial extracts.

When cancer worsens, PAMP treatment is stopped. But we know from Coley-era experiments that benefits sometimes take a long time to materialize. Instead, a fixed and not too small number of treatments should be pursued without interruption. The goal of such trials is to cure, which is admirable. But we know from other immunotherapeutic trials that sometimes a stabilization of the disease occurs, where malignant foci do not disappear but stop growing. Stabilization of disease should become an additional goal.

PAMP treatments are applied intravenously. But we have hints that stimulators of the innate immune system can be much more powerful when they are applied where the antigen is—namely close to the tumor. And in the present studies, PAMP doses are applied only a few times. It is likely that the innate immune system, lacking memory, must be stimulated again and again.

(/)

A different approach is in order. Multiple types of PAMP should be combined into a cocktail. PAMP should be injected close to tumors. If surgery is required, it might be advisable to start PAMP therapy before surgery, when antigen load is high, and continue it afterward to eradicate residual neoplasm. Fever should be allowed, if not stimulated.

On the Internet today, Coley's toxins are celebrated as an unjustly ignored therapy ready and able to cure cancers. Such simplicity is a vast overstatement, since Coley himself had very mixed results. But we have much to learn from his experiments, from the suggestive epidemiology and from the records of spontaneous regressions. It is time to integrate what they teach with our improved understanding of the innate immune system. Otherwise, the full potential of PAMP therapy will not be leveraged.

There may be prophylactic potential here as well. Epidemiological studies suggest that a personal history that includes several infections with fever sometimes significantly reduces the likelihood a person will develop cancer later (*see What the Literature Says*). One potential explanation is that feverish infections reduce would-be malignant cells. If that's true, the implications are profound.

Antibiotics must be applied immediately for life-threatening diseases such as lung infection or tuberculosis. But we must ask: Should we apply antibiotics and antipyretics (fever lowering drugs) early and for all minor infections? If we do not, more people will endure unpleasant days in bed. But quick alleviation of discomfort should be weighed carefully against the potential loss of long-term benefit.

BIBLIOGRAPHY

- Busch, W. 1867. Aus der sitzung der medicinischen. *Berliner Klinische Wochenschrift* 5:137.
- Christian, S. L., and L. A. Palmer. 1928. An apparent recovery from multiple sarcoma with involvement of both bone and soft parts treated by toxin of erysipelas and *Bacillus prodigiosus*. *American Journal of Surgery* 43:188–97.
- Coley, W. B. 1893. The treatment of malignant tumors by repeated inoculations. *The American Journal of Medical Sciences* 105:487–511.
- Coley Nauts, H., F. G. Bogatko and G. A. Fowler. 1953. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. *Acta Medic Scandinavica* 145:5–102.
- Everson, T. C., and W. H. Cole. 1968. *Spontaneous regression of cancer.* Philadelphia: J. B. Saunders & Co.
- Hall, S. 1998. *A Commotion in the Blood: Life, Death, and the Immune System.* New York: Owl Books/Henry Holt & Co. Publishing.
- Hobohm, U. 2001. Fever and cancer in perspective. *Cancer Immunology, Immunotherapy* 50:391–396.
- Hobohm, U., J. Grange and J. Stanford. 2008. PAMP in cancer immunotherapy. *Critical Reviews in Immunology* 28:95–107
- Maurer, S., and K. F. Koelmel. 1998. Spontaneous regression of advanced malignant melanoma. *Onkologie* 21:14–18.