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CHAPTER TWO

Coley

In 1999, a group of researchers compared cancer patients treated by William Coley with contemporary cancer patients and reached the following conclusion: "Given the tremendous advances in surgical techniques and medicine in general, any cohort of modern patients should be expected to fare better than patients treated 50 or more years ago. Yet no such statistical advantage for the modern group was observed in this study."[1]

In 1891, Dr. William Coley plunged a syringe into the neck of a young Italian man and carefully injected a solution of infectious bacteria. This particular type of bacteria was known to cause a skin disease called erysipelas. At the time, long before the discovery of antibiotics, erysipelas was often fatal even in a healthy person. But the young Italian man was not healthy. He

was terminally ill with cancer. Coley's intention was to produce erysipelas in the hope the patient, while recovering from the skin disease, would also recover from cancer. It was an experiment. But, as is often the case in medical research, there was an unforeseen problem. The first injection, then the second, then the third, failed to produce an infection. But Coley persisted, time after time injecting the young man with bacteria but repeatedly failing to infect him. Finally, after four months without success, an injection of a particularly virulent strain did the trick. Within an hour, the typical symptoms of a severe attack of erysipelas appeared. There was pain, nausea, a chill lasting forty minutes, and a fever that rose as high as 105°. The attack of erysipelas lasted for more than one week. By the time it subsided, the tumors had begun to break down, and within weeks the tumors had disappeared.[2] The young man returned to his home in Italy where, ten years later, he died of unknown causes.[3]

The young Italian man was only the second cancer patient treated by Coley. He had treated his first patient less than a year before. Bessie, a teenager from a prominent family, had bone cancer in her right hand. The year was 1890. Radiation had not been discovered, chemotherapy had not been dreamt of, and the only medical treatment for cancer was surgery. Coley did everything that could be done when he amputated Bessie's arm beneath the elbow but, as is so often the case with cancer, everything that could be done was not enough. The following month, lumps appeared in her breasts and lymph nodes, and Bessie was in constant, debilitating pain that could only be managed with increasingly larger doses of morphine. In her next and final month, more nodules developed, more lymph nodes

hardened, Bessie's enlarged liver turned her skin yellow from jaundice, and the cancer filled her abdominal cavity and covered her skin from head to foot. Unable to tolerate solid food, her condition steadily declined. With the young doctor at her bedside, death finally brought relief.[4]

Coley was painfully aware that surgery was rarely effective except when the cancer could be completely removed and the patient was in good physical condition, but this was exactly such a case. Bessie was healthy and her cancer was confined to the extremity of a limb. Her death had a profound impact on Coley. If the fact that his surgical skills had proven useless in this one case was troubling, the knowledge he was not equipped to face the next case was even more so.

The medical schools of the late nineteenth century, even the great ones like Harvard from which Coley graduated in 1888, taught much about anatomy, bone-setting, surgery and diagnosis, but very little about the treatment of disease. By today's standards, diseases usually went untreated. Other than morphine to dull pain, there were very few available medications. Ailments were either self-limiting or incurable. To the nineteenth century physician, his or her role was to perform practical doctoring and, when there was nothing practical to be done, to diagnose disease and to explain its probable course, positive or negative. It was all that could be expected. But Coley wanted to do more. In a personal campaign to find something that might help the next Bessie, Coley researched about 100 similar cases treated at the New York Hospital during the previous 15 years.[5] He found nothing out of the ordinary except for a peculiar

incident involving a German immigrant named Stein that had occurred seven years previously.

In 1884, the 31-year-old Mr. Stein had undergone an operation to remove a cancerous growth from his neck. It had been his fifth operation in three years and, for the fifth time, it proved impossible to remove the entire tumor. And there was more bad news to come. After two weeks confined to his hospital bed recuperating from the ineffective surgery, Mr. Stein contracted a dangerous skin disease called erysipelas. He experienced high fever, chills, nausea and pain, then, as the skin disease began to subside there was a second attack. Once more Mr. Stein was racked with fever, chills, nausea and pain, until finally, the second attack of erysipelas gradually came to an end. It was at this point that the attending physician, Dr. Bull, witnessed an extraordinary event. During the resolution of the skin disease, the wound from the operation healed along with all visible traces of the tumor. Shortly thereafter, Mr. Stein was discharged from the hospital.[6]

After this remarkable incident, there was no further mention of Mr. Stein in the records of the hospital, not even a follow up examination. After five surgeries in three years, the most reasonable explanation for the extended absence was that he had died, but no one knew for sure. Coley set out to discover what happened to Mr. Stein. Even today, it is difficult to reconstruct a patient's history seven years after the fact, but in 1891 it must have seemed an impossible task. Nonetheless, Coley searched New York's immigrant neighborhoods for someone with knowledge of Mr. Stein's ultimate fate. Then, in his own words, "After great effort I finally succeeded in tracing the after-history

of this patient and found him alive and well." Coley persuaded Mr. Stein to accompany him back to the New York Hospital where he was examined by Coley and Dr. Bull. No trace of the cancer remained.[7]

The only clinical factor that distinguished Mr. Stein's case from the others was the erysipelas infection. To Coley, it seemed obvious that the accidental infection must have somehow cured the cancer. If so, Coley reasoned, then an intentional infection might also have curative effects. Coley decided to act on his intuition. He resolved to purposely induce an attack of erysipelas in his next appropriate cancer patient. It would be something like fighting fire with fire and, in researching the bacterial cause for this new kind of fire, Coley found there were others who had come to the same conclusion before him.

In 1867, a German professor named Busch wrote what is likely the first account of an attempt to cure cancer by intentionally infecting a patient with erysipelas.[8] Busch applied the used bandages of an erysipelas patient to the neck of a 19-year-old female patient with a child-head-sized tumor. The young woman contracted erysipelas, her temperature rose to 104°F, and the huge tumor shrank to the size of a small apple within two weeks. After the erysipelas infection was cured, the tumor grew back and the woman left the clinic to an unknown fate.[9] In 1882, a German scientist named Fehleisen was the first to identify, isolate and culture the bacteria responsible for erysipelas.[10] Fehleisen injected the live cultured bacteria into seven cancer patients and achieved remissions in three of them.[11] As mentioned earlier, remission has a different meaning than regression. Tumors in a cancer that is in remission have stopped

growing, and tumors in a cancer that is in regression are becoming smaller either in number or size. In total, Coley found more than 20 published accounts before 1890 linking infections of erysipelas to remissions or regressions of cancer.[12]

In May 1891, Coley conducted his first erysipelas experiment with the young Italian man described at the beginning of this chapter as his patient. By the following year, he had treated a total of ten "inoperable and quite hopeless" cancer patients, but continued to find it difficult to produce an erysipelas infection. After his initial success with the Italian man, Coley was able to induce an attack of erysipelas in only two out of his next nine cancer patients. In these two successfully infected patients, the cancerous tumors entirely disappeared in one and reduced in size and number in the other.[13] These results were very encouraging because every patient who contracted erysipelas showed remarkable improvement. However, most patients did not contract the disease and there could be no therapy without the disease. Coley needed a more efficient method of infecting patients, and perhaps he found one because the next two consecutive patients were successfully infected. But then there was a setback. Both patients died, but not from cancer. They died from erysipelas.

The consecutive fatalities forced Coley to rethink his strategy. He needed an alternative method to deliver the beneficial effects of erysipelas without the necessity of producing the disease itself. Coley suspected the anticancer activity of his treatment was not the result of the skin disease erysipelas, but rather due to an unknown component of the bacteria that was "toxic" to the cancer. If so, it might be possible to treat patients with killed

bacteria. That way the patient would receive the benefit of the anticancer toxin without the necessity of contracting an often-fatal skin disease. These thoughts, more intuitive than scientific, led Coley to abandon the use of live bacteria and begin treating patients with killed bacteria.

In the first version of "Coley Toxins," which despite the name are not poisonous, the bacteria responsible for erysipelas were heat sterilized and passed through a porcelain filter. This version was used in four cases of inoperable cancer but failed to generate the intense symptoms such as chills and high fevers that had been observed in all successful treatments. As an experiment, a revised version of Coley Toxins was prepared that included a second type of killed bacteria known to generate intense reactions in rabbits. Coley hoped the mixture of the two types of bacteria would generate a more intense and therefore more beneficial reaction.[14]

The first patient to receive the mixed version of Coley Toxins was a sixteen-year-old boy who was bedridden with an abdominal tumor measuring six by five inches in width and about five inches in thickness. An exploratory surgery revealed the tumor to be inoperable because it involved the entire thickness of the abdominal wall and was attached to the underlying bones. A sample of the tumor was microscopically examined and found to be cancerous. Over a period of four months, every few days Coley injected his new mixed toxin directly into the tumor mass. On each injection, there was dramatic rise in body temperature and extreme chills and trembling. The tumor gradually diminished in size. At discharge from the hospital in May 1893 after four months of intensive treatment, the tumor was a fifth its original

size. Two weeks later, a small mass could be felt but it was no longer visible. By August the remains of the growth were barely perceptible. The boy returned to his regular work and received no further anticancer treatment. He remained in very good health until he died suddenly of a heart attack 26 years later.[15]

Between 1891 and 1896, Coley published 16 papers describing his method but his reports did not generate widespread excitement. At the time, most physicians practiced surgery and firmly believed there could be no cure for cancer other than surgery. Since it was impossible for Coley's treatment to be successful, surviving patients must not have had cancer in the first place. As one 1893 observer succinctly put it, "A cure by means other than surgical is … sufficient proof of a mistaken diagnosis."[16] To most members of the medical community, non-surgical approaches to the treatment of cancer were simply of little interest. The medical journals in which Coley published, however, had a wide readership. While most readers ignored Coley's articles, a number of independently minded doctors began to make use of the new cancer treatment. Before the turn of the twentieth century, at least 42 physicians from Europe and North America had reported cases of cancer that had been successfully treated with Coley Toxins.[17]

Cancer therapies have improved since Coley's day, but improvements in treatment have resulted for the most part in prolonging the disease rather than curing it. For example, when an appeal for donations on behalf of the American Cancer Society claims, "Today, far more than half of all cancers are curable,"[18] it is referring to the fact that about 60% of patients diagnosed with cancer during the period 1989-96 survived for at least five

years.[19] According to the National Cancer Institute, the five-year survival rate includes "persons who survive five years after diagnosis, whether in remission, disease-free, or under treatment".[20] This concept is far different than Webster's definition of cure as something that "heals or permanently alleviates a harmful or troublesome situation."[21]

According to the National Cancer Institute, about 60% of cancer patients survive at least five years after initial diagnosis compared to only 35% in 1950.[22] The principal difficulty with this kind of comparison is that the process of cancer diagnosis has improved over the years. Many patients seem to be surviving longer simply because their cancers are diagnosed sooner. Instead of dying in four years in the 1950s, an equivalent group of cancer patients in the 2000s might be dying in six years. In these cases, the improvement in survival is the result of better diagnosis, not better treatment. For example, in white females resident in the United States, the five-year survival of breast cancer patients during the period 1988-1997 was about 82% compared to only 64% in the period 1975-1987. That appears to be a considerable improvement. However, during 1988-1997 about 63% of breast cancers were initially detected when the disease was confined to a primary tumor compared to only 51% in the period 1975-1987.[23] The 28% increase in five-year survivability must be tempered by the fact that 24% more breast cancers were diagnosed before they began to spread.

Earlier diagnosis is the most important contributing factor in the observed increase in five-year survival rates. Only that portion of the improvement in survival rates that is independent of time of diagnosis can be rightfully credited to modern cancer therapies.

The improvement in survival due to modern cancer treatments is small but we are grateful for it. However, this improvement, encouraging as it might be, masks a fundamental problem. Modern therapies have added some years to the life of the average cancer patient, but modern therapies have not reduced the patient's chances of dying from the disease. In fact, a resident of the United States is more likely to die of cancer today (202.8 per 100,000) than in 1950 (195.4 per 100,000).[24]

The greatest value of Coley Toxins is evident through the experience of patients who received the therapy. Rather than surviving additional years with cancer, many of these patients lived the rest of their lives without cancer. For example, in December 1895 a woman was diagnosed with inoperable cancer. She had a tumor the size of an orange in her upper left breast that extended to a region under the clavicle and surrounded major blood vessels. The woman was in a rapidly declining state of health and had lost 24 pounds in the previous six weeks. Her Connecticut surgeons administered 76 injections of Coley Toxins over a period of three months and, as the tumor shrank in size, on nine occasions incisions were made into it to facilitate the drainage of dead tissue. By the end of three months of therapy, the tumor had entirely disappeared and the woman soon regained her weight and her health. She lived a normal life and died of pneumonia in her 89th year, more than 47 years after diagnosis.[25]

Progress against cancer is calculated in terms of five-year survival after diagnosis. Five years is an arbitrary, but practical, unit of measure. It might be more meaningful to measure longer-term survival, but it would be impractical in terms of patient-

tracking and reporting delays. Doctors and patients want to know the expected performance of current therapies, not the performance of historical therapies. In any case, the infrastructure that would be needed to follow the long-term medical histories of cancer patients does not exist. We must be content with an imperfect reporting system that makes no distinction between patients who survive five years and patients who enjoy the remainder of their lives without cancer.

Most patients with inoperable cancer do not survive even five years. However, even before the turn of the twentieth century some patients with inoperable cancer went on to live normal lives. In 1893, a 29-year-old woman noticed a small swelling on the left side of her abdomen that rapidly increased in size. An exploratory operation found an inoperable tumor involving much of the abdominal wall. Microscopic examination of a tumor sample returned a diagnosis of cancer of the connective tissue. Toxin therapy was begun the following month. Injections directly into the tumor were given daily for six weeks and then, after a month of rest to allow the inflammation caused by the repeated injections to subside, the therapy was continued for an additional month. Over the treatment period the tumor steadily decreased in size to the point it was no longer detectable. There was no trace of malignancy at the time of her death from heart failure in 1918, 25 years after diagnosis.[26]

After the death of her father in 1936, Helen Coley Nauts inherited her father's papers including his diaries, medical reports, case files and a correspondence numbering many thousands of letters. Her original intention was to write her father's biography but, after a meticulous reading of the archive, she found her true

vocation. For more than fifty years, the daughter labored to "rehabilitate her father's reputation and revive use of the toxins in modern medicine."[27] Thanks to the relentless detective work of Helen Coley Nauts, we now know that many of Coley's patients were long term survivors who went on to live normal lives.

For example, even with the best modern treatment, widely spread cervical cancer is a virtual death sentence with only 13% of women surviving five years after diagnosis.[28] Yet, more than 100 years ago a 43-year-old woman with widely spread cervical cancer recovered from the disease and went on to live a normal life. In her case, an exploratory surgery revealed two growths, one on each side of the abdomen, attached to the small and large intestines. No attempt was made to remove the tumors. Microscopic examination confirmed a diagnosis of inoperable widely spread cervical cancer. The woman's son was a doctor and he treated his mother at home. Coley Toxins were injected deeply into the cancerous masses twice a week for six months, then once a week for a year. Each injection resulted in a full reaction including high fever and the tumors slowly reduced in size. By the completion of the first eighteen months of therapy, the woman was able to resume her normal activities. After a period of rest, the treatments were resumed for an additional eighteen months as a precaution against reoccurrence. An extended therapeutic regimen is difficult both for the patient and the physician, but in the end it proved to be worth the effort. The woman died of pneumonia in her 79th year, 36 years after diagnosis.[29]

We owe this account to a son and a daughter. Without the son's dedication to provide his mother with long-term therapy there

would be no happy ending. Without Helen Coley Naut's painstaking research into the ultimate fate of her father's patients, the happy ending would be unknown. Sons and daughters, mothers and fathers; unlike dispassionate medical statistics, cancer is very much a family affair and the most tragic cases, and also the most heartwarming, are those involving children. There is the case of a nine-year-old girl, bedridden in a Connecticut hospital, and unable to close her mouth. The marble-sized tumor that distended her jaws could not be surgically removed. The only possible treatment was toxin therapy. Injections were given twice weekly and on each occasion the girl experienced high fever and violent chills. After two months, the tumor had completely regressed and the patient was allowed to go home where she continued to receive injections for an additional five months. The little girl grew up and remained in excellent health. She was free from recurrence when last traced in 1953, more than 46 years after diagnosis.[30]

Coley Toxins therapy was usually administered in the patient's own home. Even one hundred years ago, it was considered too expensive to tie up a hospital bed for many months at a time. The Mayo Clinic, for example, would begin toxin therapy and then discharge the patient into the care of a local doctor. In most cases, however, cancer patients were never hospitalized at all. These patients relied entirely on their family doctor. One such physician, Dr. Calkins of Watertown, New York, routinely treated his cancer patients for a full year. He would give daily injections of Coley Toxins for six months and then twice weekly for another six months. Using this technique, Calkins achieved an 80% five-year survival over a 32-year period.[31]

Another family physician, Dr. Arthur Burns of Kentville, Nova Scotia, knew he had a difficult case when a young woman's health unexplainably began to rapidly deteriorate. He referred her to a large Halifax hospital where an exploratory surgery revealed a huge mass of tumor attached to and growing outwards from her kidney. When microscopic examination returned a diagnosis of widely spread kidney cancer, her condition was considered hopeless. She was discharged from the hospital and returned to her hometown on a stretcher. Dr. Burns administered injections of Coley Toxins for six weeks and on each occasion her temperature rose to about 105°F. Her condition gradually improved and she began to gain back weight. Four months after therapy began, she returned to a normal, healthy life. When the woman was last traced in 1952, she was entirely healthy 40 years after diagnosis of widely spread kidney cancer.[32]

There are many more examples of desperately sick cancer patients who received a new lease on life after receiving toxin therapy. An extremely sick woman with widely spread ovarian cancer received fifteen months of toxin therapy beginning in 1916, and completely regained her health until she died suddenly of a cerebral hemorrhage 20 years later.[33] A patient with recurrent melanoma received injections of Coley Toxins in 1902 and remained well without further recurrence for 41 years.[34] A patient who had become paralyzed due to a massive tumor involving the spine received injections for three months in 1902, completely recovered, and lived a normal life without further recurrence for 42 years.[35] A patient with egg-sized tumors in the neck and jaw, received six months of toxin therapy in 1906 during which the tumors entirely disappeared without

further recurrence for 46 years.[36] A patient with inoperable bone cancer received six months of toxin therapy in 1909 and went on to live a normal life without recurrence for 42 years.[37]

During his career, Coley treated about one thousand cancer patients with comparable or better results than the best treatments available today. However, Coley did not understand how his therapy worked and therefore had no scientific model to guide its proper implementation. He made changes in treatment protocol based solely on personal observations. He learned it was necessary for patients to experience a strong reaction including a high fever and chills in order to benefit from the therapy. He also learned through experience that different patients required different amounts of toxin, so he began with small doses, then gradually built up the strength until he observed the desired reaction. Some of this dose-variable effect was due to the various preparations of Coley Toxins available over the years. Each contained the same mixture of two killed bacteria, but varied greatly in potency. In particular, the commercially available Coley Toxins made by Parke Davis & Company between 1899 and 1951 were often of poor quality.[38] Finally, after hundreds of patients and years of follow up, Coley learned that the therapy must be continued for some months after apparent recovery or else there was an increased risk the cancer would return.

These observations, perfectly sensible in hindsight, came slowly after years of experience. By the time Coley appreciated the importance of quality control in the manufacture of the toxins and exactly how they should be administered, he was nearing the end of his career. There were few physicians willing to revisit an old therapy without a satisfactory medical explanation, let alone

one that required months of treatment and constant surveillance, when radiation therapy was well understood and straightforward to administer. After Coley's death in 1936, the use of the toxins gradually dwindled until by the end of the 1950s, when chemotherapy was considered the anticancer treatment of the future, Coley Toxins were almost, but not quite, forgotten.

In the United States, perhaps the last recorded use of Coley Toxins as a primary cancer treatment occurred in the 1960s. In this case, a 69-year-old man with colon cancer that had spread to his liver and lungs was in such a hopeless condition he was expected to survive less than one week. As a last resort, a doctor in Oklahoma City administered eight daily doses of Coley Toxins and each time the patient experienced the healing bouts of high fever and chills. This period of treatment is far short of the amount of time usually required to assure a long-lasting response. Nevertheless, one week after completion of the toxin therapy, the man returned home, his weight and strength increased, and complete regression occurred. The man was free of disease when last traced eight years after receiving the toxin therapy.[39]

Perhaps the last recorded use of Coley Toxins as a primary cancer treatment anywhere in the world occurred in China during the 1980s. An adult male had terminal liver cancer involving large tumors in both lobes of the liver. The man received 68 injections of Coley Toxins in 34 weeks. By the end of this course of treatment, all of the tumors had completely regressed.[40]

The examples that have been described are but a small sample of the Coley Toxins cases documented in the medical literature.[41] These accounts are so compelling that readers can be easily seduced into unwarranted conclusions about the efficacy of a forgotten therapy more than one hundred years old. By themselves, Coley Toxins are not the cure for cancer. To keep a reasonable perspective, it is useful to remember that about half the time toxin therapy did not work. It can be argued that many of these failures were due to weak versions of the toxins or improper administration, but a similar argument can be made for the shortcomings of any cancer treatment. For whatever reason, Coley Toxins failed about fifty percent of the time. In that respect, this historical therapy is no better than its modern replacements. On the other hand, when Coley Toxins did work, more patients went on to live a normal life or enjoyed longer periods of disease-free survival.

For example, of 896 patients treated with Coley Toxins in one retrospective study, 33 had breast cancer. Of these patients, 13 had operable cancer that had not widely spread and all 13 survived at least five years. The remaining 20 patients had inoperable, widely spread disease. Of these, 65% survived at least five years.[42] In comparison, five-year survival of women with widely spread breast cancer at Yale-New Haven Hospital was about 7% in the 1920s and improved to about 15% in the 1950s.[43] More recently, according to the American Cancer Society, 20% of women diagnosed with widely spread breast cancer in 1989-1996 survived five years.[44]

As we have seen, Coley Toxins were a highly effective anticancer treatment. As we shall see, Coley Toxins work by stimulating a

powerful immune response. By itself, a powerful immune response is sufficient to cure some cancers in some patients but cannot cure all cancers in all patients. A powerfully stimulated immune system is only part of the answer because cancer cells are frequently able to hide from the immune system. The immune system cannot kill what it cannot see. The remaining part of the answer, training the immune system to recognize hidden cancer cells, is the subject of ongoing research that is beginning to yield tangible results. However, before we discuss the end of cancer, we must start with its beginnings.

[1] Richardson MA, Ramirez T, Russell NC, Moye LA. Coley toxins immunotherapy: a retrospective review. Alt Ther Health Med 1999; 5:42; comparison of 128 Coley cases with 1,675 controls from the official registry of the National Cancer Institute.

[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; 105:487-511.

[3] Nauts HC. Bacteria and cancer – antagonisms and benefits. Cancer Surv 1989; 8(4):713-23.

[4] Hall, Stephen S. *A Commotion in the Blood.* London: Little, Brown and Company, 1997. An excellent and readable account of Coley's life.

[5] Nauts HC. Bacteria and cancer – antagonisms and benefits. Cancer Surv 1989; 8(4):718; Coley WB. The treatment of malignant tumors by repeated inoculations of Erysipelas, with a report of ten original cases. Am J Med Sci 1893; 105:487.

[6] Coley WB. The treatment of malignant tumors by repeated inoculations of Erysipelas, with a report of ten original cases. Am J Med Sci 1893; 105:487-8.

[7] Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. Am J Med Sci 1906; 131:375.

[8] Busch W. Aus der sitzung der medicinischen section vom 13 November 1867. Berl Klin Wochenschr 1868; 5:137.

[9] Hobohm U. Fever and cancer in perspective. Cancer Immunol Immunother 2001; 50(8):391-6.

[10] Fehleisen F. Über die Züchtung der Erysipelkokken auf künstlichem Nährboden und die Übertragbarkeit auf den Menschen. Dtsch Med Wochenschau 1882; 8:553.

[11] Hobohm U. Fever and cancer in perspective. Cancer Immunol Immunother 2001; 50(8):391-6.

[12] Coley WB. The treatment of malignant tumors by repeated inoculations of Erysipelas, with a report of ten original cases. Am J Med Sci 1893; 105:487-511.

[13] Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. Am J Med Sci 1906; 131:375-430.

[14] Ibid., p 378-9.

[15] Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. Am J Med Sci 1906; 131:393-4; Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:21-2.

[16] Nauts HC, McLaren JR. Coley toxins – the first century. Adv Exp Med Biol 1990; 267:483-500.

[17] Table of Successful Cases Treated by Other Surgeons: Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. Am J Med Sci 1906; 131:422-8.

[18] American Cancer Society appeal for funding. Website of the Illinois State and University Employees Combined Appeal, http://www.secaillinois.org/acs.hlm accessed December 17, 2002.

[19] Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. CA Cancer J Clin 2001; 51:15-36.

[20] *Understanding prognosis and cancer statistics*. National Cancer Institute web site, http://cis.nci.gov/fact/8_2.htm accessed December 17, 2002.

[21] *Webster's Ninth New Collegiate Dictionary*. Markham, Ontario: Thomas Allen & Son, 1989, p 316.

[22] Table I-3, SEER Cancer Statistics Review 1973-1999. National Cancer Institute website www.seer.cancer.gov. Accessed April 2, 2003.

[23] Clegg LX, Li, FP, Hankey BF, et al. Cancer survival among US whites and minorities. Arch Intern Med 2002; 162:1985-93.

[24] Table I-2, SEER Cancer Statistics Review 1973-1999. National Cancer Institute website www.seer.cancer.gov. Accessed April 2, 2003. These statistics, by the way, have been age-adjusted to make today's numbers comparable with those of 1950; otherwise the increased chance of dying from cancer would be even greater

[25] Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:27-8; Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. Am J Med Sci 1906; 131:398-9.

[26] Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:22-5.

[27] Quote from: Hall, Stephen S. *A Commotion in the Blood*. London: Little, Brown and Company, 1998, p 118. An excellent account of Coley's life.

[28] 5-year survival in metastatic cervical cancer is 15% for white women and 7% for black women. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. CA Cancer J Clin 2001; 51:34.

[29] Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:28-30.

[30] Ibid., p 39-40.

[31] Nauts HC, McLaren JR. Coley toxins – the first century. Adv Exp Med Biol 1990; 267:486.

[32] Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:59-61.

[33] Ibid., p 75-7.

[34] Nauts HC, McLaren JR. Coley toxins – the first century. Adv Exp Med Biol 1990; 267:488.

[35] Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:30-2.

[36] Ibid., p 40-2.

[37] Ibid., p 51-3.

[38] Ibid., p 93-6.

[39] Nauts HC. Bacteria and cancer – antagonisms and benefits. Cancer Surv 1989; 8(4):718-9.

[40] Ibid., p 720.

[41] A critical analysis of 30 inoperable cases treated with Coley Toxins: Nauts HC, Fowler GA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. Acta Med Scand Suppl 1953; 276:1-103; also see extensive list of references in: Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. Pharmacol Ther 1994; 64(3):529-64.

[42] Nauts HC. Bacterial pyrogens: beneficial effects on cancer patients. Biomedical Thermology 1982; 690.

[43] Todd M, Shoag M, Cadman E. Survival of women with metastatic breast cancer at Yale from 1920 to 1980. J Clin Oncology 1983; 1(6):406-8.

[44] By race, 22% of white and 15% of black women with metastatic breast cancer survived five years. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. CA Cancer J Clin 2001; 51:15-34.