

THE TOXINS OF WILLIAM B. COLEY AND THE TREATMENT OF BONE AND SOFT-TISSUE SARCOMAS

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ABSTRACT

In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. He was successful, and this was one of the first examples of immunotherapy. Over the next forty years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. These products became known as Coley's Toxins. He and other doctors who used them reported excellent results, especially in bone and soft-tissue sarcomas.

Despite his reported good results, Coley's Toxins came under a great deal of criticism because many doctors did not believe his results. This criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxins to gradually disappear from use. However, the modern science of immunology has shown that Coley's principles were correct and that some cancers are sensitive to an enhanced immune system. Because research is very active in this field, William B. Coley, a bone sarcoma surgeon, deserves the title "Father of Immunotherapy."

Each year in the United States approximately 5000 people die from bone and soft-tissue sarcomas.^{1,2} These deaths occur despite innovative techniques in surgery, new chemotherapeutic drugs, and the sophisticated delivery of radiotherapy. Therefore, in an attempt to reduce this death rate, new treatment modalities are being investigated. One such treatment modality is immunotherapy. Immunotherapy is based on the idea that a



Figure 1. William B. Coley (1862-1936) from *Trans Am Surg Assoc* 54(1936):415. Courtesy of the Welch Library of the History of Medicine.

patient's immune system can be stimulated or enhanced to attack the malignant tumors. The first systematic study of immunotherapy for the treatment of malignant tumors was begun in 1891 by William B. Coley (1862-1936), a bone sarcoma surgeon (Figure 1). Coley injected streptococcal organisms into a cancer patient in order to cause erysipelas and stimulate the immune system. The patient's tumor disappeared, presumably because it was attacked by the immune system. This experiment began Coley's life-long study of immunotherapy. For the next 40 years, he treated hundreds of patients with inoperable bone and soft-tissue sarcomas using immunotherapy. His work was widely publicized and discussed. He was in the ideal location to carry out his work as the Chief of the Bone Sarcoma Unit at Memorial Hospital in New York, America's first cancer hospital, and his work was supported by the first cancer research grant, which he helped establish.

Not only is Coley known as the "Father of Immunotherapy," he also became the model for the present-day clinician-scientist. First he had inspiration: He was deeply moved by the death of his very first patients due to wide-

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spread metastatic bone sarcoma. Second, motivated by this inspiration, he combed the literature to find ideas about what might be an effective treatment for cancer. Some reports suggested that having an infection might cause tumor regression. Third, following his study of the literature, he developed a theory for treatment. He began to inject patients with bacteria and bacterial products and noticed that some tumors disappeared. Finally, he regularly published his work. During his life, Coley's work was often severely criticized, and, at times, he was completely dismissed by the scientific community. This occurred because his methods of treatment and patient follow-up were not consistent, and many colleagues could not believe his good results. However, Coley persisted. Thanks to recent discoveries in immunology, we are now convinced that some of his observations were correct, and that his theories may have much to offer us today.

William Coley was born in 1862 to a very old Connecticut family. He went to college at Yale and graduated from Harvard Medical School in 1888. He then joined the staff of the New York Hospital as an intern on the surgical service. One of his first patients in 1890 was Bessie Dashiell, a 17-year-old girl who had a swelling in her hand which was diagnosed as a malignant bone tumor, most probably an Ewing's sarcoma in her metacarpal. Despite a forearm amputation, she died of widespread metastases within ten weeks. This rapid spread of a lethal cancer had a profound effect on Coley. He was determined to find an effective treatment. During a review of the records of New York Hospital, Coley learned about a patient who, seven years previously, had had an inoperable malignant tumor in his neck that seemed to disappear after he developed erysipelas. The patient was discharged, apparently without evidence of a residual tumor. Coley personally searched for this patient by combing the tenements of Lower Manhattan. After weeks, he finally found the patient, a German immigrant named Stein, and he had no evidence of residual cancer.

Mr. Stein's seemingly miraculous cure contrasted with Bessie Dashiell's rapid death and inspired Coley to scour the literature looking for other patients who had cancer remission due to a concurrent bacterial infection. He was aware of anecdotal theories of the beneficial effect of fever on malignant tumors. For example, Diedier noted in 1725 that patients with syphilis developed very few malignant tumors.³ Sir James Paget had also mentioned that an infection may cause a regression in certain tumors.⁴ In addition to these anecdotes, Coley was able to find specific examples in the literature. For example, in 1867, the German physician Busch reported that a malignant tumor had disappeared when the patient contracted erysipelas. The cause of erysipelas, a streptococcal organism, was not known until 1881.⁵ Then, in

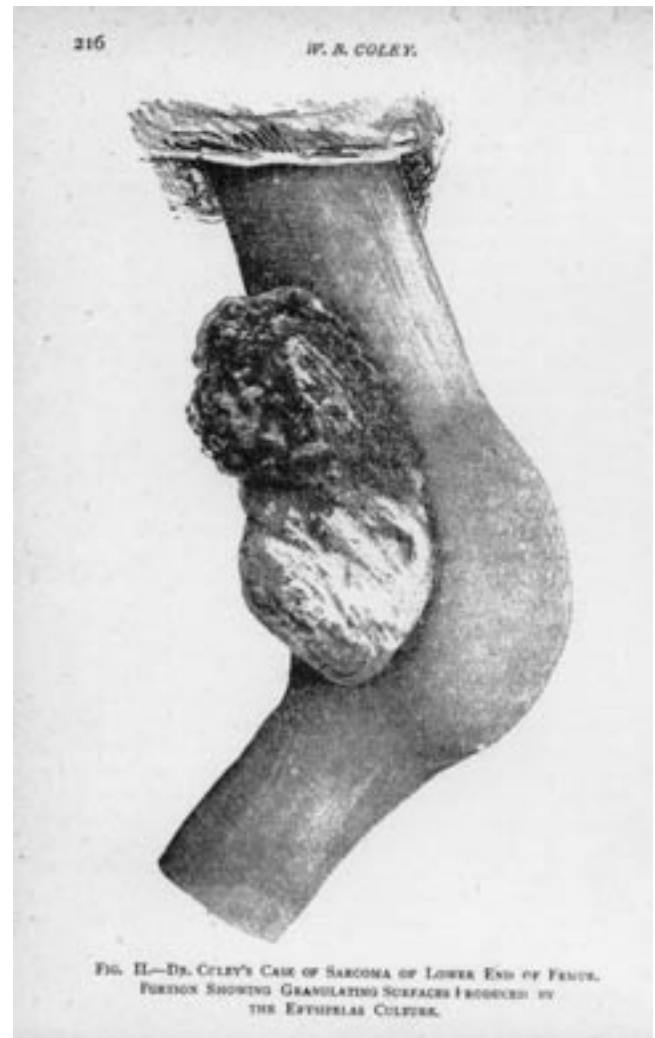


Figure 2. Drawing of Coley's first bone sarcoma case treated with his toxins. Courtesy of *Annals of Surgery*/Lippincott.

1888, Bruns intentionally injected a cancer patient with the streptococcus organism to induce erysipelas, and he noticed the shrinkage of the malignancy.⁶ Coley was able to find approximately 47 cases in the literature documenting the beneficial effect of infections on tumors.

Coley was convinced that having a severe infection could cause cancer to regress. It took a great deal of courage, but in 1891 he injected his first patient with streptococcal organisms and noticed the shrinkage of a malignant tumor. This encouraged him to treat two other patients with long-bone sarcomas (Figure 2). The injections appeared to be quite dangerous, and two of his patients died of infection. However, there was some observable shrinkage of their malignant tumors. He published his first work describing these three patients in 1891 (Figure 3).⁷

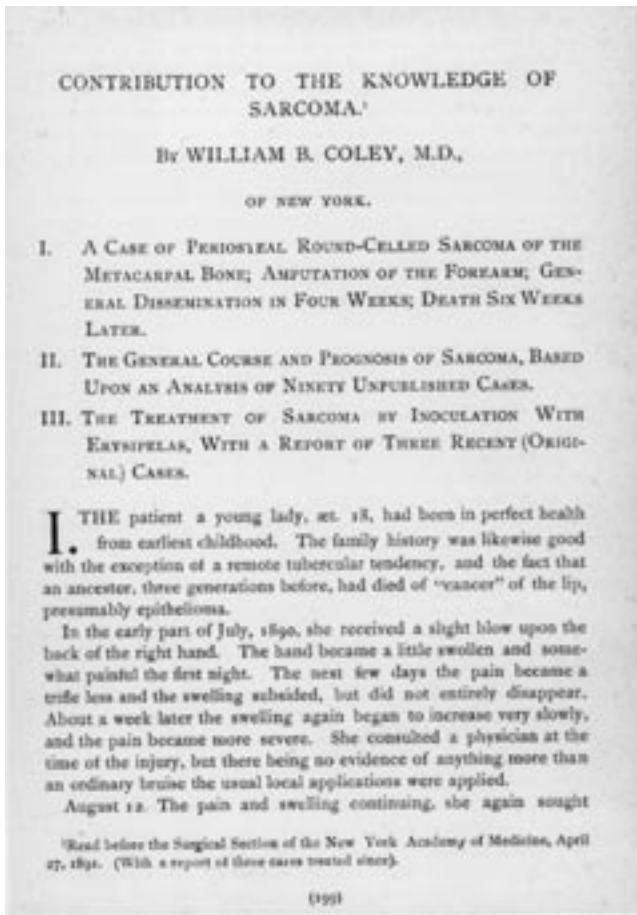


Figure 3. Title page to Coley's first article of 1891 describing his toxins. Courtesy of *Annals of Surgery*/Lippincott.

Because of the danger of live streptococcal organisms, Coley continued his treatments using a heat-killed streptococcal organism combined with a second organism that we now call *Serratia marcescens*. This concoction became known as Coley's Toxin. By 1893, he had tried his toxin on ten patients, most of whom did well.⁸ By 1916, he had documented 80 more cases in a monograph.⁹ By the end of his career, he had written over 150 papers on this subject and treated almost 1,000 cases. He mainly used his toxins on patients with inoperable bone and soft-tissue sarcomas, observing that this treatment was far less effective on other types of cancer such as melanomas and carcinomas. Beginning in 1899, Parke Davis & Company had begun to prepare the toxins so they were available for all physicians. They were widely used for the next 30 years.¹⁰

As a result of his widely used treatment, as well as the fact that he was publishing his work, Coley was much in the public eye. Early in his career he received small donations from the Rockefeller family to help with his

research, and in 1902 he arranged a large grant from the Huntington family that supported him and other cancer researchers. This endowment was the first in the United States designated specifically to study cancer.¹¹

Despite Coley's high profile, his work came under criticism because of inconsistencies. First, although Coley described hundreds of favorable responses to his toxins, his patient follow-up was poorly controlled and poorly documented. Second, there were 13 different preparations of the toxins, and some of these were more effective than others. Third, Coley used various methods of administration. Some toxins were given intravenously, others intramuscularly, and some were injected directly into the tumor. Therefore, many doctors who used Coley's Toxin did not get the same good results that he did, and some noticed no effect at all. Some critics went so far as to call him a charlatan. As early as 1894, the *Journal of the American Medical Association (JAMA)* issued a severe criticism of the use of these toxins:

*There is no longer much question of the entire failure of the toxin injections, as a cure for sarcomata and malignant growths. During the last six months the alleged remedy has been faithfully tried by many surgeons, but so far not a single well-authenticated case of recovery has been reported.*¹²

Despite JAMA's claim, however, some physicians had success with Coley's Toxin. Yet many of those doctors looked askance at Coley because of his personal belief, held long after the idea had been generally dismissed, that cancer was caused by microorganisms. Coley held this belief until the end of his career.

Additional controversies surrounding Coley's work reflect a field struggling to stabilize its understanding of how to treat cancer. For example, James Ewing, perhaps the most famous cancer pathologist in the country, was a leading opponent of Coley's work. This was a particular problem for Coley because Ewing was Medical Director of Memorial Hospital, and for many years was Coley's boss. Their memos to one another reflect constant interpersonal animosity. Ewing himself had become a fanatical supporter of radiation therapy for the treatment of all bone tumors and repudiated any other theories for the treatment of cancer. Ewing therefore refused Coley permission to use his toxins at Memorial Hospital. This was ironic, because Coley had more experience than any other surgeon in the country in treating the small round blue cell sarcoma that still carries Ewing's name.

In addition, by 1920 Coley's work ran into serious resistance from the Bone Sarcoma Registry. This registry, established by E. A. Codman, who had invited Ewing

and Joseph Bloodgood from Johns Hopkins to join him, was the first cancer registry of any kind.¹³ Its role was to standardize the diagnosis and treatment of all forms of bone cancer by collecting cases from all over the country. The cases would be evaluated by Codman, Ewing, Bloodgood, and other prominent bone specialists. Coley had a great deal of difficulty having some of his cases accepted by the registry, despite being the leading bone tumor surgeon in the country. Members of the registry believed the toxins were ineffective. In fact, during the 1920s, both Codman and Bloodgood insisted that the excellent responses reported by Coley were often because the patients had the wrong diagnoses.

Thus, his work gradually fell out of favor. By 1952, the Park Davis Company no longer produced Coley's Toxin, and, in 1962 the Food and Drug Administration refused to acknowledge Coley's Toxin as a proven drug.¹⁴ Thus, in 1962 it became illegal to use Coley's Toxins for the treatment of cancer.

Despite the downward spiral of Coley's treatment ideas, they never completely died. He himself remained undeterred, holding on to his belief in his toxins until the end of his career in 1933. He was not alone. In fact, by the early 1930s, a few doctors had changed their minds and were willing to accept that the toxins might be beneficial. In 1934, The Journal of the American Medical Association reversed its position and agreed that Coley's Toxin might be of value:

*It appears, that undoubtedly the combined toxins of erysipelas and prodigiosus may sometimes play a significant role in preventing or retarding malignant recurrence or metastases; occasionally they may be curative in hopelessly inoperable neoplasms; . . . The Council has, for these reasons, retained Erysipelas and Prodigiosus Toxins-Coley in New and Nonofficial Remedies, with a view to facilitating further studies with the product.*¹⁵

In a symposium held in 1935, Codman, apparently seeing evidence of the toxin's benefits, reversed his position and suggested that Coley's treatment might have some value after all.¹⁶ Also, a controlled study done in 1962 showed a dramatic response in 20 of 93 cancer patients.¹⁷ Further acceptance of his ideas was brought about by Coley's own children. His son Bradley (1892-1961), also an orthopaedic surgeon, succeeded him as the head of the Bone Tumor Service at Memorial Hospital. Bradley Coley's major textbook on bone tumors was published in 1948, and while advocating surgery as the main treatment for bone sarcomas, he supported the use of Coley's toxin as adjunctive therapy.¹⁸ He believed that it would be of value in preventing micro-metastasis. His daughter, Helen Coley Nauts (1907-2001), became

a cancer researcher and devoted her life to the study of her father's toxins. She tabulated every patient he treated and reviewed all his notes. She published 18 monographs and tabulated over 1000 of his cases and noticed that in 500 of these there was near-complete regression.¹⁹

Nowadays, orthopaedic oncologists do not use Coley's Toxins for the treatment of bone and soft-tissue sarcomas. However, because many of these tumors are lethal, treatment options may one day be supplemented by immunotherapy. Since Coley's death, the field of immunology has developed into a sophisticated specialty. Scientists are studying the effect on tumors of such factors as tumor necrosis factor (TNF), interferons, streptokinase and many other cytokines, all related to the immune system.²⁰ Indeed, vaccines are being developed for the treatment of numerous types of cancer, particularly colon cancer and melanoma.²¹ One form of immunotherapy which is consistently effective is the installation of BCG bacilli into the bladder to treat superficial bladder cancer.

William Coley's intuitions were correct: Stimulating the immune system may be effective in treating cancer. He was a model of the clinician-scientist, treating patients and using his practice to initiate research and build theories. But he was a man before his time, and he met with severe criticism. Despite this criticism, however, Coley stuck with his ideas, and today we are recognizing their potential value.

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