

# Coley's toxins in perspective

Charlie O. Starnes

**Despite initial hopes, the efficacy of tumour necrosis factor in treating cancer patients has been disappointing. But a more careful selection of patients, and more appropriate treatment, might be fruitful.**

EVERY year, about 3,000 people in the United States who have soft-tissue sarcomas die. The history of tumour necrosis factor (TNF) shows that one-tenth of these patients could have been saved by treatment with a bacterial vaccine. Although certainly considerably less than perfection, such odds would provide hope for an otherwise inoperable patient. In view of recent, predominantly disappointing results achieved with conventional therapies and biological products such as recombinant cytokines, a new perspective on TNF is warranted.

The history of our experience with TNF and cancer begins with the observation that certain cancer patients who developed concurrent bacterial infections would also experience concomitant remissions of their malignant disease. Recognition of this phenomenon dates back into the 1700s, about 100 years before the New York surgeon William B. Coley engineered a large-scale effort to take advantage of this observation to the benefit of his patients. Coley's interest in the subject stemmed from the loss of his first cancer patient, a young girl with a sarcoma in her right arm. Despite Coley's radical surgery, the girl developed metastatic disease and died shortly thereafter. Coley investigated the medical records of the hospital and found a seven-year-old record of a patient with a four-times recurrent inoperable sarcoma of the neck, but who was stated to have experienced a regression of the disease under the influence of an erysipelas infection (a superficial, streptococcal infection of the skin). Coley located this patient, and found him free from any clinical evidence of malignancy. He then found a substantial number of publications containing similar observations, the most frequent combination of infectious disease and cancer being erysipelas in sarcoma patients.

As a result of this encounter, Coley began the deliberate induction of erysipelas in his cancer patients, with the obvious intent of bringing their malignant disease under control. In an era before the availability of antibiotics, the problems associated with this approach soon became obvious: erysipelas was not easy to control once it began and, perhaps surprisingly, it was not all that easy to induce in the first place, some patients requiring repeated injections and others never developing the disease.

Although some dramatically definitive results were achieved, the difficulties that Coley encountered led him to the use of heat-killed versions of the streptococcus, beginning in 1892. The use of these products gave only minor therapeutic effects, and Coley decided to incorporate *Bacillus prodigiosus* (now called *Serratia marcescens*) into his vaccine, with the original idea of enhancing the virulence of the streptococcus, the two organisms being grown together in the same flask. Although this line of reasoning was later shown to be



**Coley — pioneer of vaccine therapy.**

erroneous (the organisms were later grown separately and then admixed), it was apparently an important step towards achieving reproducible therapeutic effects in the clinic. This combination of Gram positive, heat-killed streptococcus plus Gram negative, heat-killed *S. marcescens* is commonly referred to as "Coley's toxins", and gave Coley and his contemporaries most of their clinical successes<sup>1</sup>.

Coley's therapy was not easy for the patient. Within an hour after injection, the patient experienced a shaking chill lasting from 10–15 minutes, followed by development of a fever in the range of 102–105 °F. Although these symptoms would subside in 12–24 hours, patients were given the injections daily or every other day for weeks to months, gradually tapering off depending on how well treatment was tolerated, and the response of the malignant disease. Despite the adverse effects, an appropriately selected patient had a reasonable chance of long-term survival (see table).

The table shows that patients with soft-tissue sarcomas are represented far more frequently (about 50%) than they occur within the human cancer population as a whole (by today's standards, only about 0.6%), and that this population of patients gave most of the dramatic responses, or 'cures' tabulated in column E. It is explained throughout the older literature that such patients were deliberately selected, as it became obvious to Coley and his contemporaries that patients with this form of the disease responded far more frequently and dramatically to the therapy than did other (unfortunately more common) forms of cancer. As Coley himself stated, "During the first few years, I treated a considerable number of cases of inoperable carcinoma . . . While in most cases a certain amount of improvement was apparent . . . in the great majority it was . . . only temporary and I decided to restrict the method chiefly to inoperable sarcoma"<sup>2</sup>, and later on, in reference to his clinical results achieved by 1909, ". . . if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumor cells of one variety of cancer — sarcoma — it is not unreasonable to suppose that by the use of some other forms of bacterial toxins we may succeed in destroying or inhibiting the growth of the other and more common variety — carcinoma"<sup>1</sup>. One of Coley's contemporaries, the Harvard physician T. W. Harmer, independently stated that the therapy "should be instituted in no case unless proven microscopically to be sarcoma"<sup>3</sup>. Coley himself reached this decision first, in 1897, and nearly 100 years later we have come to make that decision again.

After Coley's death in 1936, clinical interest in the use of his vaccine diminished in preference to the more broadly applicable chemotherapy and radiation, and it is not difficult to understand why. With these modalities it was no longer necessary deliberately to select a small subpopulation of cancer patients. Years later, when it became evident that long-term control of the disease was not being achieved, there was a renewed interest in clinical use of the vaccine<sup>4</sup>, which has rightly persisted<sup>5</sup>. Unfortunately, the necessity of selecting patients was no longer appreciated: less than 10% of the patients treated in recent times have

SUMMARY OF PATIENTS TREATED WITH COLEY'S TOXINS BEFORE 1940

Type of cancer	Total	A	B	C	D	E
Soft-tissue sarcomas	104	38	12	17	15	22
Lymphosarcomas (lymphomas)	50	24	7	4	7	8
Osteosarcoma	3	2	1	0	0	0
Ovarian carcinoma	4	1	2	0	0	1
Cervical carcinoma	2	0	1	0	0	1
Testicular	18	10	2	3	2	1
Renal	6	3	0	1	1	1
Multiple myeloma	1	0	0	1	0	0
Colorectal carcinoma	2	1	1	0	0	0
Breast carcinoma	14	8	4	2	0	0
Melanoma	6	2	3	0	1	0

Evaluation restricted to those patients considered inoperable at the time of treatment, and who had received no therapy other than the vaccine. Individual patient records are as follows: A, those making no beneficial response to treatment; B, those making an initial response but either known to relapse or lost to follow-up with 5 years; C, those rendered free of disease but lost to follow-up between 5 and 10 years; D, those rendered free of disease but lost to follow-up between 10 and 20 years; E, those rendered free of clinical evidence of disease for at least 20 years. (Source of figures is a series of articles by H. C. Nauts and G. A. Flower in the *Cancer Research Institute Monograph* between 1969 and 1975.)

been those with soft-tissue sarcomas. In addition to the lack of appropriate selection, most of the patients in these studies had received chemotherapy, radiation or both, some even receiving chemotherapy in combination with the vaccine. More recent evidence suggests that patients undergoing chemotherapy can sustain lasting alterations in various immunological parameters which can persist for 18 months after the therapy ends<sup>6</sup>, and may well be permanent. Given the immunological dependence of endotoxin therapy that has been described in various animal models<sup>7</sup>, it may have been to Coley's advantage not to have had such confounding elements to contend with.

Such problems may also be contributing factors to the recent lack of success in the clinical use of recombinant TNF and related cytokines, as most patients entering such trials have previously failed standard therapy and, for the most part, no deliberate attempt has been made to select sarcomas. The lone exception has been a study by Demetri *et al.*<sup>8</sup>, who initially treated a series of 36 pathologically unselected patients with a combination of TNF and interferon- $\gamma$ . Because the only therapeutic responses were observed in patients with sarcoma, Demetri *et al.* deliberately selected such patients for further study; in a subsequent phase II trial, two additional responses were observed<sup>9</sup>. Although this decision bears obvious analogy to that made by Coley in 1897, the degree of responses observed by Demetri *et al.* was of far less magnitude than that achieved by Coley. The most likely explanation for the difference is the complexity of the patient's immune response to continuous and aggressive administration of bacterial vaccine, which would undoubtedly elicit a cascade of cytokines.

Why sarcomas should preferentially respond to Coley's treatment is an important and unresolved issue. Most sarcomas are derived from mesenchymal

tissue which is located anatomically within the mesodermal germ layer of a developing embryo. The term carcinoma does not imply embryonic derivation, rather that a malignancy has arisen from an epithelium, which in turn can originate from either endodermal, ectodermal or mesodermal germ-cell layers. In retrospect, it may be that the mesodermal embryonic origin of the tumour is the more important prognostic factor, to serve as a common denominator between the soft-tissue sarcomas and lymphosarcomas or lymphomas, which although classified pathologically as separate and distinct diseases, responded to Coley's treatment in a similar fashion; together they accounted for about 90% of the permanent responses. Further, most of the relatively few known permanent responses observed in patients with carcinoma were seen in tumours arising in tissues of mesodermal origin (see table). Coley was not the attending physician in these cases, but such responses prompted him to state in 1936, "... the number of cases of inoperable carcinoma apparently cured by the toxin treatment administered by other surgeons led me to the belief that I had greatly underestimated the value of the toxins in these cases"<sup>2</sup>.

Indeed, if the mesodermal embryonic origin of the tumour does turn out to be an important prognostic factor for the prediction of responses to this form of therapy, then the population of treatable patients could well be substantially larger than Coley realized, including those with renal, ovarian and other mesodermally derived carcinomas. More recent experience with the vaccine in pathologically unselected patient populations may tend to substantiate this hypothesis; at least one dramatic response has been witnessed in a 38-year-old woman with ovarian carcinoma<sup>4</sup>.

The comparative sensitivity of tumours of mesodermal origin to TNF-

related therapy has been a recurrent theme ever since the initial observations of erysipelas-induced regressions in patients with sarcomas. After Coley's death, the animal models used most often in the study of this subject have been predominantly sarcomas: Carswell *et al.*<sup>10</sup> used a sarcoma in the initial discovery of TNF; Berendt *et al.*<sup>7</sup> used sarcomas to describe the essential importance of tumour immunogenicity and a corresponding T-cell immune response to the curative effects of endotoxin therapy; McIntosh *et al.*<sup>11</sup> have used a different series of sarcomas to extend these observations to combination therapy with TNF, interleukin-2 and interferon- $\alpha$ . It is consistent with the medical records of Coley's patients, as well as current observations in animal models, to postulate that sarcomas and other malignancies of mesodermal origin may have a higher probability of being immunogenic.

The obvious implications are twofold. Most important, serious consideration should be given to a return to an aggressive use of the vaccine in the appropriately selected patients, the optimal profile being a patient with inoperable soft-tissue sarcoma or lymphoma and no prior therapy; treatable patients may also include those with ovarian and other mesodermally derived carcinomas. Better patient selection would also undoubtedly be provided by the development of methods and procedures for establishing tumour immunogenicity in humans. Second, laboratory efforts should be concentrated on a search for the identification of a factor or factors made in response to Coley's vaccine which would have more therapeutic relevance than those that we currently possess, but perhaps to be used in combination with them. In the light of the predominantly disappointing results with chemotherapy in the treatment of the advanced stages of cancer, such an approach is certainly a reasonable place to concentrate our efforts. □

Charlie O. Starnes is at Amgen, Inc., 1840 Dehavillard Drive, Thousand Oaks, California 91320-1789, USA.

1. Coley, W. C. *Fractitioner* **20**, 539-545 (1898).
2. Nauts, H. C. *et al. Can. Res.* **6**, 205-216 (1946).
3. Harmer, T. W. *Boston Med. Surg. J.* **171**, 253 (1914).
4. Johnston, B. J. & Novales, E. T. *Can. Chem. Rep.* No. 21, 43-68 (1962).
5. Axelrod, R. S. *et al. Cancer* **61**, 2219-2230 (1988).
6. Tichatschek, E. *et al. Can. Immun. Immunother.* **27**, 278-282 (1988).
7. Berendt, M. J. *et al. J. exp. Med.* **148**, 1560 (1978).
8. Demetri, G. D. *et al. J. clin. Oncol.* **7**, 1545 (1989).
9. Spriggs, D. R. & Yates, S. W. in *Tumor Necrosis Factors* (ed. Beutler, B.) 394 (Raven, New York, 1992).
10. Carswell, E. A. *et al. Proc. natn. Acad. Sci. U.S.A.* **72**, 3666-3670 (1975).
11. McIntosh, J. K. *et al. Can. Res.* **49**, 1408-1414 (1989).

ACKNOWLEDGEMENT. I thank Helen Coley Nauts for her efforts in collecting and compiling the medical records of her father's patients.