Spontaneous regression: a hidden treasure buried in time

S. A. Hoption Cann,[1,2,3] **J. P. van Netten,**[1,2] **C. van Netten,**[3] **D. W. Glover**[1]

[1]Special Development Laboratory, Royal Jubilee Hospital, Victoria, British Columbia, Canada; [2]Department of Biology, University of Victoria, Victoria, British Columbia, Canada; [3]Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada

Summary   Spontaneous tumor regression is a phenomenon that has been observed for hundreds, if not thousands of years. Although the term spontaneous implies 'without apparent cause', a review of case reports over the last several hundred years demonstrates that regression generally coincides with acute infections. Observations of this non-specific effect led to the emergence of active cancer immunotherapies by the 1700s. By the 1890s, William Coley refined this approach with a bacterial vaccine which, when administered properly, could induce complete regression of extensive metastatic disease. Unfortunately, after Coley's death, his vaccine and technique fell into obscurity.

Modern approaches to treatment have reduced the occurrence of spontaneous regressions. Aseptic techniques and antibiotics significantly reduce postoperative infections, while chemotherapy and radiation impair immune activation even when an infection does occur.

More than a century after its inception, Coley's vaccine and aggressive approach to treatment may still be one of most effective immunotherapies for cancer. © 2002 Harcourt Publishers Ltd

INTRODUCTION

In a recent review of current immunotherapy regimens, it was stated that 'immunotherapy applied to patients with established tumors rarely leads to an objective response' (1). Yet historically, tumor regression associated with an immune response was not an unusual phenomenon. Why is this regression not observed in association with current immunotherapy regimens?

Although numerous cases of so-called spontaneous tumor regression have been published over the last several hundred years, such reports have become rare in current medical literature. Virtually all of these reports note regression concomitant with infections, including diphtheria, gonorrhea, hepatitis, influenza, malaria, measles, smallpox, syphilis and tuberculosis, as well as various

other pyogenic and non-pyogenic infections (2). An early example was a case reported by Le Dran (3) in 1742. A 15-year-old patient had an extensive inoperable cancer of the left breast. The tumor ulcerated and gangrene developed. Within 2 days the entire tumor sloughed off with profuse hemorrhaging and later suppuration. The wound healed after 5 weeks. However, the disease recurred, causing death 8 months later. Similarly, Trnka (4) in 1783 described a patient with breast cancer who developed tertian malaria (associated with chills, fever and sweating). The illness was associated with a complete remission after few weeks. Benefits arising from such intratumoral infections was not an uncommon observation, as the physician Quesnay (5) stated of one patient: 'this mortification could have been advantageous to the patient, for it could, as we have seen sometimes, destroy the whole tumor, procuring a salutary amputation without pain.'

THE EMERGENCE OF IMMUNOTHERAPY

Coincidental infections were probably the impetus for the active use of pathogens as a cancer treatment. An example was reported by White (6) in 1768 as 'the

wonderful method of curing cancers by means of toads,' where he describes a woman from Hungerford, England, who treated patients with breast cancer. The method required that a toad be applied to the breast lesion until its death (7). Reportedly, the dead toad would be allowed to remain on the breast lesion by the application of a poultice for several weeks. Pennant (8) provides the details of one such case, a woman with metastatic breast cancer who had been 'reduced to a meer skeleton.' Her left side and stomach were swollen and a tumor on her neck made swallowing difficult. Without surgery and after several months of toad treatment, however, her metastatic lesions abated and she was able to swallow with ease. In 1752, Amoureaux (9) treated a patient with an ulcerated malignant breast by applying a septic dressing. The patient developed a fever and severe inflammation with suppuration; complete regression was noted in 4 weeks. Similarly, other physicians were known to deliberately establish multiple 'issues' (suppurating sores) following cancer surgery. These issues were generally situated in the tumor, its periphery or in the arms (10,11). An analogous method was used by Verneuil (12). After cancer surgery, he would leave the incision open or loosely approximated with drainage, where suppuration would then ensue. A student of Verneuil made the following observation: 'I was often struck by the slowness with which recurrence developed in such cases…I asked myself if suppuration, in eliminating the traces of cancer which had escaped the knife, did not play a role in delaying recurrence, and if therein lay the secret of success' (13). In addition to these treatments, some investigators induced tumor regression by injecting patients with other infectious agents such as malaria (14) and syphilis (15,16).

These basic 'immunotherapies' gained some general acceptance in the 1800s. In his treatise on breast cancer, Tanchou (17) commented: 'it is remarkable that after hemlock it is gangrene that caused the largest number of cures. Gangrene may be considered as a therapeutic agent, whether it occurs spontaneously or is induced medically.' Similarly, Walshe (18), in his text on cancer treatment, viewed such therapy as a practical application of a phenomenon that had been observed for centuries, and concluded that 'the inoculation of the matter of common and hospital gangrene has been practiced, with the design of imitating the natural processes of cure.' Cruveilhier (19) also promoted these measures, stating that a beneficial inflammation may be produced spontaneously or: 'induced by incisions or irritating applications. There results a melting away or gangrene of the affected tissues, followed by complete sloughing and a radical cure.' However, as a result of the growing popularity of Lister's methods for aseptic surgery in the late nineteenth and early twentieth century (20), septic

'immunotherapy' soon fell into disfavor among cancer surgeons who failed to appreciate its therapeutic value. Thus, as the prevention of postoperative infections gained further acceptance, the idea that cancer surgery should be distinct from other types of surgery was lost.

'INFECTION' WITHOUT AN INFECTION

William Coley, a surgeon at New York Memorial (Sloan-Kettering) Hospital, was the first researcher to make a systematic study of the entire immunotherapy approach and would eventually treat the largest series of patients in this manner. Unaware of the previous work in this area, Coley noted a coincidental tumor regression in a patient who developed a streptococcal infection within an ulcerated tumor. Based on this observation, he attempted to reproduce these results by infecting his cancer patients with this same bacterium, previously known as erysipelas (21). Although he achieved some success, in the pre-antibiotic era problems associated with this approach soon became apparent. 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 required repeated injections and others never developed an infection. Subsequently, Coley developed a vaccine consisting of extracts of killed Gram-positive *Streptococcus pyogenes* and Gram-negative *Serratia marcescens*, which became known as 'Coley's toxins' (22). These toxins produced many of the symptoms of bacterial infections, such as fever and chills, without the need to worry about producing an actual infection.

Throughout his career Coley stressed that the technique of administration was essential to its curative effect, while the precise formulation was of secondary importance – he used more than 15 different formulations during his career. Martha Tracy, a researcher who made many of the vaccine formulations for Coley and who experimented with a wide range of killed bacterial vaccines on animal tumors, observed that the most effective formulations were those that induced both local and systemic reactions (23).

A key aspect that Coley found to be necessary for tumor regression was the induction of a mild to moderate fever. He would thus gauge dosage levels according to individual patient responses and increase the dose as necessary to avoid vaccine tolerance. To simulate the effects of a chronic infection in his patients, he would inject the tumor vicinity daily or every other day for the first month or two. Other factors that he found crucial to a patient's long-term survival included direct vaccine injection into the tumor or metastases, and a prolonged follow-up to prevent recurrence (24). Ensuring a prolonged follow-up was the most difficult aspect. Due to space limitations, patients would often be referred to

their personal physician after a week to one month of treatment. In general, these physicians, and in many cases the patient, would not fully comprehend the importance of follow-up treatments or how these treatments should be carried out.

At present, the only conventional treatment analogous to Coley's technique is bacillus Calmette–Guerin (BCG) treatment of bladder cancer. Like Coley's approach, this treatment uses the whole bacterium, it is applied directly to the tumor, it produces both a local and systemic response, its effects persist after administration (because it is a live bacterium), and prolonged administration improves recurrence-free survival (25). Yet unlike Coley's approach, BCG therapy uses a live bacterium and disseminated infections, which can often be serious, occasionally occur.

Other interesting observations by Coley were that the toxins led to a marked relief of pain, so that patients could often discontinue using narcotics; and, as these injections often followed surgery or were injected into ulcerated tumors, there was an extraordinary enhancement of wound healing and even bone regeneration (22). Similar observations on infectious amelioration of cancer pain and enhancement of wound healing has been reported by others (5,12,26).

Although Coley is often credited as the father of cancer immunotherapy, few modern investigators have ever closely examined his results. A recent retrospective analysis compared patients treated with Coley's toxins (1890–1960) to that of patients from the Surveillance Epidemiology End Result (SEER) registry (1980s) for cancers of the breast, ovaries, kidneys, and soft-tissue sarcomas (27). In comparing treatment with Coley's toxins to the SEER registry, the authors concluded that the risk of death within 10 years was not significantly different for any of the cancers studied. These results are rather surprising considering the fact that Coley's vaccine was developed at only a nominal cost, that most cases were considered inoperable, and that this experimental work began over 100 years ago.

SIDE-EFFECT OR IMMUNE RESPONSE?

Use of Coley's toxins is not an easy treatment for the patient. In addition to the fever and chills, a patient might experience other symptoms such as loss of appetite, fatigue, and depression. In part, these symptoms were due to the vaccine, and in part to toxemia arising from the rapid tumor regression, where necrotic tumor constituents would enter the bloodstream.

The symptoms described above are also known to occur in conjunction with some current immunotherapies (28–31). Unfortunately, modern investigators often consider such immune responses 'side-effects' (28,30,31),

failing to recognize their value in tumor regression and generally seeking ways to minimize or eliminate these symptoms. Little consideration is given as to whether such side-effects improve patient survival.

Decline in the use of Coley's toxins came about after Coley's death in 1936. By the 1950s, antibiotics came into general use for surgery, greatly reducing the chance of infection following tumor excision. Furthermore, radiation and chemotherapy became mainstays of treatment as they required less individualization and the immediate results were more predictable, although it soon became apparent that such treatments often led to cures of a short duration. Chemotherapy, and to varying degrees radiation, is highly immunosuppressive, and therefore infections in the cancer patient cause little immunostimulation, and in any case, are rapidly treated with antibiotics. Thus, it is not surprising that reports of spontaneous regression have become rare. Still, an association with acute infections prevails in the few recent reports of this phenomenon (32–34).

THE DUAL ROLE OF THE IMMUNE SYSTEM

In recent years, histological studies have established that solid tumors and their metastases are infiltrated by large numbers of immune cells (35–37). Yet, morphological alterations of tumor cells suggestive of leukocyte-induced damage are absent or extremely rare – despite the close contact generally observed between leukocytes and tumor cells. Thus, in spite of the innate ability of the immune system to induce tumor regression, the cytotoxic activity of these tumor-infiltrating leukocytes (TIL) is compromised. We have suggested that this is primarily due to the fact that the immune system has two major functions: *defense* and *repair* (38). The well-studied defensive role may become active during acute infection, where cytotoxic cells seek out and destroy invading pathogens. Although the reparative process following wounding is also well-known, less emphasis has been placed on the role the immune system plays in mediating this process (39). In fact, a considerable volume of research in this area has confirmed that TIL not only fail to inhibit growth, but also actively aid tumor progression through their reparative functions (37,40–43).

How can the immune response be so erratic? An example that highlights this duality in function was discussed by Williams (44) in 1898. He noted a conspicuous antagonism between active tuberculosis and cancer, stating 'it is certainly most exceptional to find both diseases in active progress in the same individual. The outbreak of cancer often follows or coincides with the healing of pulmonary tubercle, although, in most cases, the intervening period is fairly protracted.' In an analysis of 11 195 autopsy examinations, Carlson and Bell (45) noted that
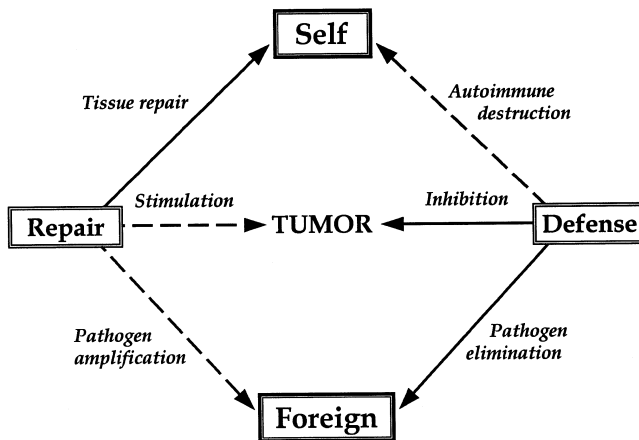
Fig. 1 Diagram showing the two aspects of immune response to self and foreign antigens. A malignancy expressing both self and foreign moieties can elicit an abnormal response from the host. A defensive response to infection may concomitantly suppress tumor growth, while sterile trauma at the tumor site (blunt trauma, surgery, etc.) may stimulate growth. Normal responses (solid lines), abnormal responses (dashed lines).

tuberculosis was of a similar prevalence in those with and without cancer. However, in confirming Williams's observations, they found *active* tuberculosis to be 'strikingly less' in cancerous than non-cancerous subjects. The preceding example illustrates that the same infection can stimulate or allow either immune defensive or reparative responses, which correspondingly may suppress or augment tumor growth (Fig. 1). Thus, within the confines of tumorous lesions, an opportunity exists; strategically located immune cells lie awaiting the appropriate stimuli necessary for reactivating their defensive capabilities (38).

IMPLICATIONS FOR TREATMENT

Most of the early, yet often successful, forays into cancer immunotherapy have been forgotten. A recent review of cancer vaccines described spontaneous regression as being 'often mentioned – rarely observed' (46). Such comments illustrate how little is presently known of the underlying causes of 'spontaneous' tumor regression, as well as those factors which inhibit it – aseptic surgery, antibiotic usage, chemotherapy and radiotherapy.

In his published papers, Coley repeatedly emphasized factors that he found to be vital for successful treatment (i.e. daily injections, direct tumor injection, and a prolonged follow-up) – points that appear lost to modern researchers. Despite the 'crude' approach taken by Coley, his vaccine stimulated a complex immune response that could induce the complete regression of both extensive primary and metastatic lesions. Furthermore, his vaccine was universally effective against many types of malignancies. Tumors that were observed to partially or

completely regress following treatment with Coley's vaccine included: lymphomas, melanomas, myelomas, sarcomas and a wide spectrum of carcinomas (2,22,24).

How is this relevant to modern cancer therapy? Despite the seemingly rudimentary nature of the vaccine, the immune system has evolved to generate an elaborate response involving a multitude of factors secreted in sequentially precise order and concentration following exposure to infectious agents. Modern investigations have shown how difficult it is to reproduce this complex immune response, and correspondingly tumor regression, when more precise tumor-specific antigens and cytokines are used (47). In contrast to such immunotherapies, Coley's vaccine could be produced at a nominal cost, be used for a wide spectrum of cancers, and still provide a significant benefit to patients at all stages of disease. His approach should now become a challenge to modern immunotherapy investigators. Applying our current knowledge of the immune system to Coley's approach will allow the fine tuning, monitoring and careful control of this procedure, while providing new insights into pain control, healing, and tumor regression.

REFERENCES

1. Forni G., Lollini P. L., Musiani P., Colombo M. P. Immunoprevention of cancer: is the time ripe? *Cancer Res* 2000; **60**: 2571–2575.
2. Nauts H. C. The Beneficial Effects of Bacterial Infections on Host Resistance to Cancer: End Results in 449 Cases, 2nd edn. Monograph No. 8. New York: Cancer Research Institute, 1980.
3. Le Dran H. F. Traité des opérations de chirurgie. Paris: C. Osmont, 1742.
4. Trnka V. History of remittent fevers. Vienna: Vindobonae, 1783.
5. Quesnay F. Traité de la gangrène. Paris: d'Houry, 1749: 313.
6. White G. Letter XVIII to Thomas Pennant, 27 July 1768. In: The Natural History of Selborne. London: G. Routledge and Sons, 1890: 56.
7. Goldsmith O. An history of the frog kind. In: An history of the earth and animated nature. London: J Nourse, 1774, vol. 7: 102–107.
8. Pennant T. British Zoology. London: Warrington, 1777, vol. 3: 338–344.
9. Amoureaux A. On the internal usage of belladonna. *J Med Chir Pharm* 1760; **13**: 47–65.
10. Dupré de Lisle M. Treatise on the cancer disease. Paris: Couturier, 1774.
11. Vautier A. H. General perspectives on the cancer illness. *Thèse du Paris*, 1813, No. 43.
12. Verneuil A. Inoculation of erysipelas as a means of cure. *Union Med (Paris)* 1886; **41**: 19–22, 217–221.
13. Thiery P. On fulguration in cancer. *Bull Mem Soc Chir Paris* 1909; **35**: 604–698.
14. Rovighi A. Cancer and malaria. *Lavori Cong Med Int (Rome)* 1903; **12**: 202–204.
15. Alquié A. Syphilis inoculation in cancer. *Gaz Hop* 1851; **24**: 546.
16. Didot A. Essai sur la prophylaxie du cancer par la syphilization artificielle. *Bull Acad R Med Belg* 1851, 1852; **11**: 100–172.
17. Tanchou S. Research on the medical treatment of cancerous tumors of the breast, work based on three centuries of

observations (extracts from a large number of authors). Paris: G. Baillière, 1844.

18. Walshe W. H. The nature and treatment of cancer. London: Taylor and Walter, 1844.

19. Cruveilhier J. General treatise on pathological anatomy. Paris: J. B. Baillière, 1864; vol. 5: 251.

20. Lister J. The collected papers of Joseph, Baron Lister. Oxford: Clarendon Press, 1906.

21. Coley W. B. 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.

22. Nauts H. C., Fowler G. A., Bogatko F. H. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumours in man. *Acta Med Scand Suppl* 1953; **276**: 1–103.

23. Beebe S. P., Tracy M. The treatment of experimental tumors with bacterial toxins. *JAMA* 1907; **49**: 1493–1498.

24. Coley W. B. 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.

25. Lamm D. L., Blumenstein B. A., Crissman J. D. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. *J Urol* 2000; **163**: 1124–1129.

26. Mohr C. A case of carcinoma of the breast vs. erysipelas and arsenic. *North Am J Homeop* 1888; **3**: 700–702.

27. Richardson M. A., Ramirez T., Russell N. C., Moye L. A. Coley toxins immunotherapy: a retrospective review. *Altern Ther Health Med* 1999; **5**: 42–47.

28. Brivio F., Lissoni P., Fumagalli L. et al. Pre-operative IL-2 immunoprophylaxis of cancer recurrence: long-term clinical results of a phase II study in radically operable colorectal cancer. *Oncol Rep* 1999; **6**: 1205–1207.

29. Rosenstein D. L., Lerner D., Cai J. More on the depressive effects of interferon alfa. *N Engl J Med* 1999; **341**: 849–850.

30. Vermorken J. B., Claessen A. M. E., van Tinteren H. et al. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. *Lancet* 1999; **353**: 345–350.

31. Yano T., Sugio K., Yamazaki K. et al. Postoperative adjuvant adoptive immunotherapy with lymph node-LAK cells and IL-2 for pathologic stage I non-small cell lung cancer. *Lung Cancer* 1999; **26**: 143–148.

32. Bowles A. P. Jr, Perkias E. Long-term remission of malignant brain tumors after intracranial infection: a report of four cases. *Neurosurgery* 1999; **44**: 636–642.

33. Garcia-Rayo S., Gurpide A., Vega F., Brugarolas A. Spontaneous tumor regression in a patient with multiple myeloma: report of another case. *Rev Med Univ Navarra* 1996; **40**: 41–42.

34. Ruckdeschel J. C., Codish S. D., Stranahan A., McNeally M. F. Postoperative empyema improves survival in lung cancer: documentation of a natural experiment. *N Engl J Med* 1972; **287**: 1013–1017.

35. Hanada T., Nakagawa M., Emoto A., Nomura T., Nasu N., Nomura Y. Prognostic value of tumor-associated macrophage count in human bladder cancer. *Int J Urol* 2000; **7**: 263–269.

36. Salvesen H. B., Akslen L. A. Significance of tumor-associated macrophages, vascular endothelial growth factor and thrombospondin-1 expression for tumor angiogenesis and prognosis in endometrial carcinomas. *Int J Cancer* 1999; **84**: 538–543.

37. van Netten J. P., Ashmead B. J., Cavers D. et al. Macrophages and their putative significance in human breast cancer. *Br J Cancer* 1992; **66**: 220–221.

38. Oleszczuk J. J., van Netten J. P., Ross A. S. Biological aspects of breast cancer metastasis: consequences of tumor cell/macrophage interactions. *Klin Perinatol Ginecol* 1994; **12**: 215–221.

39. van Netten J. P., Cann S. A. Compression mammography and breast cancer: should pain be ignored? *Cancer J* 1996; **9**: 278–279.

40. Elgert K. D., Alleva D. G., Mullins D. W. Tumor-induced immune dysfunction: the macrophage connection. *J Leukoc Biol* 1998; **64**: 275–290.

41. Takahashi Y., Bucana C. D., Liu W. et al. Platelet-derived growth factor in human colon cancer angiogenesis: role of infiltrating cells. *J Natl Cancer Inst* 1996; **88**: 1146–1151.

42. Takanami I., Takeuchi K., Kodaira S. Tumor-associated macrophage infiltration in pulmonary adenocarcinoma: association with angiogenesis and poor prognosis. *Oncology* 1999; **57**: 138–142.

43. van Netten J. P., George E. J., Ashmead B. J. et al. Macrophage-tumor cell associations: a factor in metastasis of breast cancer? *J Leukoc Biol* 1993; **54**: 360–362.

44. Williams W. R. The influence of other diseases upon cancer. *Edinburgh Med J* 1898; **4**: 334–337.

45. Carlson H. A., Bell E. T. A statistical study of the occurrence of cancer and tuberculosis in 11,195 post mortem examinations. *J Cancer Res* 1929; **13**: 126–135.

46. Dalgleish A. G. Cancer vaccines. *Br J Cancer* 2000; **82**: 1619–1624.

47. Lee K.-H., Wang E., Nielsen M.-B. et al. Increased vaccine-specific T cell frequency after peptide-based vaccination correlates with increased susceptibility to in vitro stimulation but does not lead to tumor regression. *J Immunol* 1999; **163**: 6292–6300.