REVIEW

Dr William Coley and tumour regression: a place in history or in the future

S A Hoption Cann, J P van Netten, C van Netten

Postgrad Med J 2003;**79**:672–680

Spontaneous tumour regression has followed bacterial, fungal, viral, and protozoal infections. This phenomenon inspired the development of numerous rudimentary cancer immunotherapies, with a history spanning thousands of years. Coley took advantage of this natural phenomenon, developing a killed bacterial vaccine for cancer in the late 1800s. He observed that inducing a fever was crucial for tumour regression. Unfortunately, at the present time little credence is given to the febrile response in fighting infections—no less cancer.

Rapidly growing tumours contain large numbers of leucocytes. These cells play a part in both defence and repair; however, reparative functions can also support tumour growth. Intratumoural infections may reactivate defensive functions, causing tumour regression.

Can it be a coincidence that this method of immunotherapy has been ''rediscovered'' repeatedly throughout the centuries? Clearly, Coley's approach to cancer treatment has a place in the past, present, and future. It offers a rare opportunity for the development of a broadly applicable, relatively inexpensive, yet effective treatment for cancer. Even in cases beyond the reach of conventional therapy, there is hope.

See end of article for authors' affiliations

Correspondence to: Dr S A Hoption Cann, Department of Health Care and Epidemiology, University of British Columbia, 5804 Fairview Avenue, Vancouver, BC, Canada V6T 1Z3; stephen.hoption.cann@ubc.ca

Submitted 15 July 2003
Accepted 20 August 2003

THE BONE SURGEON

''Drugs can only repress symptoms: they cannot eradicate disease. The true remedy for all diseases is Nature's remedy .... There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes. Drugs are a delusion''. So goes the counsel of physician Sir Bloomfield Bonington in George Bernard Shaw's 1906 play *The Doctor's Dilemma*.[1] Prophetic words, indeed, that may be the basis for a new paradigm in cancer treatment as we enter the 21st century.

William Coley began his career as a young surgeon at New York Memorial Hospital. Similarly disillusioned with conventional medicine, he wondered whether nature indeed held a cure for cancer. Could he harness the power of the immune system to the benefit of his cancer patients? His search for a new approach began after the loss of his very first patient in 1891. A young woman of 17 had injured her right hand and presented with persistent inflammation and pain. He diagnosed her lesion as a sarcoma of the bone and opted for amputation of her right arm below the elbow. Yet, despite no clinically evident metastases, the patient succumbed to her disease two and a half months after surgery. Shaken by this failure, Coley searched the hospital records for previous cases to learn more about this uncommon disease.

Serendipitously, he discovered the record of an immigrant patient who presented with an egg-size sarcoma on his left cheek.[2] The sarcoma was operated on twice and still recurred as a 4.5 inch grape-like cluster below his left ear. The extensive wound after surgery could not be closed and skin grafts were unsuccessful. Ironically, this failure to close the wound would play a key part in the patient's eventual cure. The tumour progressed and a final operation only partially removed the tumour. The case was considered hopeless. After the last operation, the wound became severely infected with erysipelas (that is, *Streptococcus pyogenes*) and the patient developed a high fever. Little could be done to stop the infection, yet surprisingly, after each attack of fever the ulcer improved, the tumour shrank, and finally disappeared completely. The patient was discharged four and a half months later. Coley, eager to find this patient, spent weeks searching throughout New York's lower east side. His efforts were not in vain. The patient, still bearing a large scar from his previous operations, had no trace of cancer and claimed excellent health since his discharge—seven years previously.

Coley suspected that somehow the infection was responsible for this miraculous cure. He resolved to put his theory to the test and infect his next suitable case with erysipelas. In fact, he infected his next 10 patients.[2 3] Problems with this approach soon became apparent: sometimes it was difficult to induce an infection, other times there was strong reaction and the disease regressed, however, occasionally the infection was fatal. Due to its unpredictability, he elected to switch to a vaccine containing two killed bacteria: *S pyogenes* and *Serratia marcescens*. Experimental work at the time suggested that the latter bacteria increased the virulence of the former.[4] In this way, he could simulate an infection (for example, inflammation, chills, fever) without worrying about the risks of an actual infection. This vaccine became known as ''Coley's toxins''. His first case was a success,[4] a man bedridden with an inoperable sarcoma

Abbreviations: BCG, bacillus Calmette-Guerin; IL, interleukin; TNF, tumour necrosis factor

involving the abdominal wall, pelvis, and bladder. The disease regressed completely and the patient was followed up until his death from a heart attack 26 years later.[5]

Coley worked in the Bone Service at the hospital, later becoming its chief in 1915. Thus, the majority of malignancies he treated were sarcomas. Success with Coley's vaccine, however, was by no means limited to this tumour type. Contrary to what has been suggested by others,[6 7] Coley's vaccine was widely and successfully used by other contemporaries for sarcomas as well as carcinomas, lymphomas, melanomas, and myelomas.[5 8–11] A striking feature of his immunotherapy regimen was that even when applied to patients in their final stages of disease some remarkable recoveries were obtained, with patients often outliving their cancer (box 1).[5 9–13] Coley himself went on to treat hundreds of patients, and over time, gained an appreciation of how this regimen could be most effectively administered. In fact, Coley was considered to have treated more sarcoma patients than any other physician up to that time.[14] Coley considered several points crucial to a patient's survival.[15] First and foremost was to imitate a naturally occurring acute infection, and thus, inducing a fever was essential. Injections were optimally administered daily (or every other day) for the first month or two. To avoid immune tolerance to the vaccine, the dosage was gradually increased over time (depending on patient response). The vaccine was injected directly into the primary tumour and metastases, when accessible. Finally, a minimum six month course of weekly injections was followed to prevent disease recurrence.

Shortly before Coley's death in 1936, Coley's vaccine received an endorsement in the *New and Nonofficial Remedies* of the American Medical Association, which stated ''its use as a prophylactic in conjunction with conservative or radical surgery'' and ''inoperable cases may be quite justified''.[9] In addition, some textbooks from that period advocated the use of Coley's vaccine. For example, the 1931 edition of *Modern Surgery* advised, ''after removing a sarcoma in any region, the patient should be given courses of injections of Coley's fluid''.[16] Similarly, in *Modern Operative Surgery*,[17] it is stated for sarcomas that ''after amputation, prophylactic injections of Coley's fluid should be given in doses sufficient to cause a sharp febrile reaction''.

It is often believed that Coley's vaccine was more effective against sarcomas than carcinomas.[18 19] This is due to the fact that Coley primarily treated sarcomas (not surprising considering his specialty) and because Coley initially had less success in treating carcinomas in his early experiments with streptococcus cultures.[10] Coley, however, later changed his views as his successes against carcinomas,[20–22] and those reported to him by others,[5 23] accumulated. In an analysis of 896 patients with microscopically proven malignancy treated with Coley's vaccine,[10] the five year survival for inoperable carcinomas (34%–73%) was similar to inoperable sarcomas (13%–79%), the range varying with tumour subtype.

In an effort to evaluate past successes using Coley's regimen to that currently observed with modern conventional treatment, a retrospective study compared the 10 year survival rates of patients treated by either method using data from the Surveillance Epidemiology End Result cancer registry.[24] Limitations of the study included sample sizes and staging of patients treated with Coley's vaccine. Still, this study found that despite the billions of dollars spent to develop modern cancer treatments, patients receiving modern conventional therapies did not fare better than patients receiving the treatment initiated by Coley over 100 years ago. Where would cancer treatment be today if equivalent effort and funds had been used to develop a better understanding of the treatment pioneered by Coley? Some answers might be found by taking a closer look at the history of spontaneous regression.

Box 1: The country vet

The patient, a veterinary surgeon, was struck over the right superior maxilla by the horn of a bull in February 1901. Several weeks later, he experienced severe pain over the site of injury and to relieve the pain a tooth was pulled. The pain persisted, and in April, the patient was diagnosed as having a mixed cell sarcoma.

Excision of the upper jaw was performed in May. A large tumour was found occupying the maxillary antrum and almost the entire upper jaw. The growth was too extensive for complete removal. There was also an egg-size mass under the left ear. Several days after surgery, the sarcoma began to increase in size, invading the nose and extending along the palate into the pharynx and invading the parotid region.

At this time the patient had difficulty retaining food. His speech was difficult to understand. Although previously able to walk several miles, he now could barely walk from his bed to the door. Jaundice was pronounced; the liver was enlarged. Nausea and vomiting increased. His pulse was between 140–150 beats per minute and was weak and intermittent. Although sceptical, the patient's physician, O K Winberg agreed to treat him with Coley's vaccine. In August, starting at a low dose, he gave the patient daily injections while gradually increasing each subsequent dose. Initially, he injected into the upper and lower jaw and later into the abdominal wall. By this time, the patient's disease progressed to the point where he could no longer take nourishment. He was 113 lbs. The patient had severe abdominal pain; his eyesight began to fail. His teeth became so tightly closed that it was impossible to cleanse his mouth and his speech was almost incomprehensible. He fell into a stupor, but during a brief period of consciousness, he implored to Winberg ''either kill me or cure me''.[13]

Although gradual at first, improvement became increasingly marked after his first fever. Jaundice disappeared after three weeks. By September, he was attending to a large veterinary practice, which often called him away both night and day. By that time the patient weighed 143 lbs. No trace of tumour could be found in the neck, face, or jaw. Abdominal examinations showed nothing abnormal. He continued to receive injections through to January 1902.

The patient remained in good health and free from recurrence until 1907, six years after treatment, when he died of acute nephritis from alcoholic excess.

SPONTANEOUS REGRESSION IN HISTORY

Peregrine Laziosi (1265–1345), having been afflicted with cancer himself, was several centuries later canonised and named the patron saint of cancer patients. In the course of his untiring work preaching, converting and reconciling sinners, he noticed a large growth emerging on his leg. The growth on his tibia was pronounced unanimously by the best physicians of his time to be malignant.[25] His only option was to have his leg amputated. The lesion grew to the point where it broke through the skin and became severely infected. In fact, it was stated ''such a horrible stench was given off that it could be endured by no one sitting by him''.[26] Miraculously, by the time he was due to have his operation, his physician was astonished to observe that there were no signs of the tumour. Saint Peregrine's cancer never returned. Was this spontaneous regression an isolated event or did the infection play a part?

Once Coley's interest in tumour regression was kindled, he found that spontaneous regression in association with acute infections was often mentioned in the historical literature[2] and he was to record many more cases himself.[15] Moreover,

he discovered that many past physicians had used these infections to the advantage of their patients. Such coincidental infections had in fact inspired a wide variety of rudimentary cancer immunotherapies. The earliest example of such cancer immunotherapy may be thousands of years old. In the writings of the Ebers Papyrus (c 1550 BC), attributed to the great Egyptian physician Imhotep (c 2600 BC), the recommended treatment for tumours (swellings) was a poultice followed by incision.[27] Such a regimen would inevitably lead to an infection at the tumour site. By the 1700 and 1800s AD, crude forms of cancer immunotherapy became widely known and accepted.[8] For example, Tanchou in his comprehensive treatise on cancer published in 1844, provides insight on how these immunotherapies came into being: ''One knows that often the affected lymph nodes and primary growths disappear during the course of concurrent illness, never to return. It is according to that idea … that a large number of observers have advised establishing 'issues' [suppurating sores] on diverse portions of the body and even in the wounds remaining after operation''.[28] He goes on to cite many cases from other physicians where ''issues'' were successfully established. Other strategies from that era included applying septic dressings to ulcerated tumours,[28 29] or deliberately introducing infections such as erysipelas,[30 31] gangrene,[28 32–34] or syphilis.[35 36] Until Coley produced his killed vaccine, using live bacteria to initiate an infection was a precarious gamble between life and death.

The tide began to turn against ''Nature's remedy'' for cancer during the 20th century. Firstly, cancer surgery, like any other operation, became a sterile procedure after acceptance of Lister's aseptic techniques in the late 1800s.[37] In fact, in a 1909 discussion paper on cancer treatment,[38] one surgeon suggested that the postoperative infections that were common in the past improved survival and should be encouraged. Yet in this new era, his suggestion was harshly criticised as ''a doctrine that would make surgery go backwards''. Secondly, by the time of Coley's death in 1936, radiotherapy had become an established cancer treatment, and chemotherapy was rapidly gaining acceptance. These treatments could be more easily standardised than Coley's approach and the hope that these therapies would eventually lead to a cure for cancer was high. Such therapies ran counter to immunotherapy, as they are highly immunosuppressive. Thirdly, following World War II, antibiotic use during and after surgery became commonplace. Thus, postsurgical infection rates were reduced even further, in addition to diminishing the severity and duration of those infections that did occur. Finally, once the immune system became ''redundant'' in fighting infections, antipyretics came into routine use to eliminate the discomforting symptoms of an immune response. Hence, reports of spontaneous regression have become less commonplace, although an association with acute infections is often noted when it occurs.[39–50] In fact, a retrospective study by Ruckdeschel *et al* found that patients who developed empyema after lung cancer surgery had a significantly better five year survival (50% *v* 18%).[51] Nature exists in a delicate balance, the immune system being no exception. Attempts to create an increasingly sterile environment may further reduce our innate cancer curing ability, until we may finally convince ourselves that it never existed at all.

IMMUNE SYSTEM AND DISEASE

Febrile immune response

As mentioned previously, Coley asserted that fever induction was a key aspect of his treatment. In fact, he observed that a strong febrile reaction was the symptom most associated with tumour regression. A retrospective study of patients with inoperable soft tissue sarcomas treated with Coley's vaccine found a superior five year survival in patients whose fevers averaged 38–40℃, compared with those having little or no fever (<38℃) during treatment (60% *v* 20%).[52]

With the current widespread use of antibiotics to treat infections and antipyretics to ''manage'' symptoms of an infection, the critical part played by fever is often overlooked. In hospital settings, fever is frequently suppressed as a matter of routine.[53 54] Many modern immunology texts make little mention of fever,[55–57] and may disregard it as being ''insignificant''[55] or refer to it as a ''mystery''.[56] Is the febrile immune response inconsequential to the outcome of an infection?

Historically, fevers were not only considered beneficial, but were actively encouraged. For example, Native Americans were known to treat acute febrile diseases with sweat baths.[58] In North Africa, it was observed that fevers were treated by sweating induced by hot sand or hot water baths.[58] Similarly, the great medical historian Celsus (1st century AD) described how patients with febrile illnesses would be ''well covered up to excite at the same time a violent heat and thirst''.[58] Such practices, interestingly, would reinforce the immune response to infection as it reduces the considerable amount of energy expended on fever generation and maintenance. In the late 1800s, the meticulous studies of Carl Wunderlich on febrile illnesses (over one million observations) demonstrated the diagnostic and prognostic value of continued temperature observations.[59] He also concluded that the intensity of fever was a reliable measure of disease severity, underscoring its importance in fighting disease. Recent studies support his observations,[60–62] although the ability to mount a fever in response to infection is diminished in the elderly.[63–65]

During this past century, the 1927 Nobel Prize for medicine was awarded to Julius Wagner-Jauregg for devising an ingenious fever therapy for dementia paralytica (that is, neurosyphilis). Surprisingly, or maybe not so surprisingly, his adventitious discovery arose in an analogous manner to Coley's. As a newly practising psychiatrist in 1883, he was to observe a woman patient who ''spontaneously'' recovered from a severe mental illness after an attack of erysipelas.[66] Eager to learn more about this unexpected coincidence, he undertook a comprehensive and exploratory review of the literature.[67] He discovered that the spontaneous remission of psychoses had been reported after a wide spectrum of febrile illnesses. Often remissions were temporary, although reported cures were not exceptional. In contrast to Coley who initially used live bacteria, Wagner-Jauregg began experimenting with derivatives of killed bacteria (tuberculin and later staphylococci) in treating neurosyphilis, but was dissatisfied with the reaction to these agents. However, he noted that the treatment was most effective when some febrile illness intervened.[68] He then modified his treatment by injecting patients with tertian malaria (associated with recurrent fevers), which could be controlled to a certain degree with quinine and arsenicals. Due to the intricate nature of the treatment, cure rates were variable. Remissions to the extent that patients were able to return to work were in the range of 55%–65%.[69] Gross mortality ranged from 1%–10%,[69–71] with approximately half being due to neurosyphilis.[70] Untreated, death generally occurred within several years of the diagnosis of dementia paralytica.[72] Tens of thousands of patients were eventually treated in this manner before penicillin came into common use.[73] On his efforts to use an infectious agent as treatment for neurosyphilis, Wagner-Jauregg asserted ''We have listened to nature; we have attempted to imitate the method by which nature itself produces cures''.[74]

Fever is in fact a highly conserved physiological response to infectious stimuli. It is more than just a rise in body temperature and not analogous to hyperthermia (that is, mechanically achieved increase in temperature). Hyperthermia, increasingly being applied in combination with radiotherapy and

chemotherapy,[75] has been of limited use as it lacks the systemic effects obtained with Coley's vaccine. In contrast to hyperthermia, fever is accompanied by diverse immunological changes; notably, biochemical reaction rates increase, and leucocyte proliferation, maturation, and activation is enhanced.[76 77] Febrile thermogenesis (for example, chills, shivering, etc) is associated with an increase in the metabolic rate by 2–3 times, while fever maintenance has been associated with a 30%–50% increase in the metabolic rate.[78 79] Thus, due to the substantial energy expenditure required for a febrile immune response (for example, increased heart rate, oxygen consumption, and metabolism), it is unlikely that such a response would be conserved unless it had considerable adaptive value.[79] Even animals that cannot generate a fever (for example, fishes, amphibians, reptiles) exhibit heat seeking behaviour during an infection.[80] Moreover, this heat seeking behaviour in infected animals corresponds to significantly improved survival over animals prevented from such behaviour.[81] Similarly, in animals that can generate fevers during infection, such as mammals, antipyretic administration impairs pathogen clearance and reduces survival compared with untreated animals.[82–89]

Human studies conducted in this area provide similar support for the concept that fever enhances host defence against infections. For example, retrospective studies found that paralysis incidence and severity after polio infection was more severe in children who received antipyretics.[90] Another study, in children with malaria, found that antipyretic drug therapy significantly impaired plasma clearance of the malarial parasite compared to untreated individuals.[91] Studies of children with chickenpox[92] and upper respiratory infections[93] found that antipyretic use was associated with an increased duration and severity of illness. In studies where subjects were experimentally infected with rhinovirus, antipyretic use was associated with increased viral shedding,[94] nasal signs and symptoms,[95] and duration of disease,[95] while antibody responses were reduced.[95] In those subjects infected experimentally with influenza A and *Shigella sonnei*, antipyretic therapy was associated with a significantly increased duration of illness.[96] Finally, several reports have suggested an association between the use of non-steroidal anti-inflammatory drugs and progression of invasive streptococcal infections, particularly necrotising fasciitis,[97–99] and the occurrence of empyema after pneumonia in children.[100]

One unexpected observation by Coley was the salutary effect of fever on cancer pain.[5] This beneficial property had been observed by others in association with infection-induced tumour regression.[23 101–104] In fact, patients would often reduce or discontinue their use of narcotic pain medications while receiving treatment. This phenomenon appears to be independent of tumour regression, as it often occurred immediately after vaccine injection, preceding such regressions. Lagueux, after many years of experience using Coley's vaccine, commented that ''pain always disappeared after the first injections''.[5] Actually, this remarkable analgesic effect has long been noted. The well known description of inflammation by Celsus is followed by a largely unappreciated observation on the benefits of fever: ''Now the signs of an inflammation are four: redness and swelling with heat and pain … if there is pain without inflammation, nothing is to be put on: for the actual fever at once will dissolve the pain''.[105]

Mechanisms of tumour suppression

Coley's published papers on cancer regression associated with his mixed bacterial vaccine stimulated others to explore the underlying mechanisms of this phenomenon. Specifically, researchers strived to identify the ''active'' component of Coley's vaccine.[106 107] This also led to investigations to determine which host factors produced in response to the vaccine could induce tumour regression. Cytokines such as tumour necrosis factor (TNF), interleukins, and interferons were considered as possibilities.[108–110] However, the answer is far more complex than ascribing the response to one or another factor. Any immune response to pathogens is associated with a multitude of cytokine cascades, which in turn triggers other cascades and a diversity of cellular responses. This immune cascade was readily evoked through the use of Coley's crude bacterial vaccine, but difficult to reproduce with single cytokine therapy. For example, the most effective treatment for superficial bladder cancer,[111] bacillus Calmette-Guerin (BCG), is presently the only conventional bacterial vaccine in use. Unlike Coley's treatment, BCG is not administered with the intent of inducing a fever. Furthermore, the BCG vaccine contains a live attenuated strain of bacteria (*Mycobacterium bovis*), and thus, must necessarily be used more cautiously to avoid disseminated infections.[112 113] Yet, similar to Coley's approach, the vaccine is applied directly to the tumour site and repeated courses following initial therapy (as Coley recognised over 100 years ago)[4] reduces recurrence.[114] After intravesical administration of this vaccine, a wide range of cytokines become detectable in the urine including interleukin-(IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-18, interferon-γ, interferon-γ inducible protein-10, macrophage colony stimulating factor, and TNF-α.[115–121] Many more cytokines are upregulated, others downregulated, to varying degrees throughout the course of treatment; yet, this illustrates the point that individual immunomodulating cytokines are in fact only one small facet of this complex immunological response to infection, and correspondingly, tumour regression. Thus, it becomes clear why the effectiveness of BCG is limited to superficial bladder cancer. The heat and immune activation associated with local inflammation is analogous to a scaled down systemic febrile response, and correspondingly this local response is only effective in the immediate region where it occurs. To strike at invasive cancer, a systemic response is necessary, although such a strategy would undoubtedly be hazardous as BCG is a live vaccine.

Some interesting facets of spontaneous regression include both the broad diversity of organisms that have been observed in association with this phenomenon (for example, bacterial, fungal, viral, and protozoal pathogens) and the speed at which this reaction can occur.[8 10 11 50 122] It has been proposed that the cell mediated (that is, type 1) immune response, rather than the humoral (that is, type 2) response, is a key mediator of cancer regression.[123] Yet, many of the cases of spontaneous regression as well as tumour inhibition in animal studies involved infections that elicit a humoral immune response (for example, aspergillus,[50] malaria,[11] trichinella,[124] trypanosoma[125]). Moreover, while tumour regression was often noted within hours of tumour injection with Coley's vaccine,[5] primary adaptive immune responses are often delayed by several days to a week.[126] In fact, Coley's experience[5 15] and an exploratory evaluation of case reports of spontaneous regression[8 10 11] support the concept that infection-stimulated tumour regression generally results from a ''non-specific'' innate immune response. In cases where the regression was partial and the acute or febrile phase of the infection subsided, residual tumour generally regrew.[11] Similarly, if the infection recurs or is reintroduced, tumour regression may proceed as before.[10 11] Coley stated that daily injections should be given, if the patient could bear it, as discontinuing the vaccine even for a few days would often lead to regrowth of residual tumour[15]—again suggesting that specific antitumour immunity was not a primary mechanism of this vaccine. An important mediator of the innate immune response is the Toll-like receptor family, primarily expressed on macrophages and dendritic cells.[127] These receptors both

guide the course of the innate defensive response, as well as shape the reparative response. It would appear that the antigenic complexity of Coley's vaccine was inadvertently an important factor in its success as it triggered many Toll-like receptors essential for a defensive response.

Observations that a wide spectrum of pathogens can induce tumour regression suggest that there are some unifying characteristics of the innate immune response responsible for this phenomenon. The immune system has an important *dual* role in maintaining the integrity of the host. The immune system is primarily recognised for its role in defence against foreign pathogens; however, it plays an equally important part in tissue repair. During wound healing, leucocytes are actively engaged in matrix degradation, growth factor production, and the induction of new blood and lymphatic vessels.[8 128–131] If the wound is sterile, cytotoxic defensive functions do not become activated.

A tumour, however, being partly ''self'' and partly ''foreign'', can elicit a reparative growth-promoting response from intratumoural leucocytes.[8] Based on the results of our previous research on human cancers,[128 132 133] we devised a model of this duality in function, illustrating how the immune system may either enhance or inhibit tumour growth (fig 1). Like wounds, expanding tumours release chemokines and other cytokines that attract leucocytes and signal that increased oxygen and nutrients levels are required.[8 134] In this way, an aberrant and detrimental reparative response is generated, where the immune system essentially supports tumour growth.[128 135] Leucocytes, particularly macrophages, are present in large numbers in many rapidly growing tumours.[8 128 132] Macrophages are versatile and resilient phagocytes capable of prolonged survival in the acidic wound environment.[136] Moreover, macrophages contribute to the production, mobilisation, activation, and regulation of all immune cells.[137] There is even evidence that monocyte/macrophages can differentiate into endothelial progenitor cells[138 139] and fibroblasts.[128 129] Interestingly, tumour-derived fibroblasts have been shown to stimulate tumour cells in vitro, an effect not observed with normal tissue fibroblasts.[140] Thus, macrophages can play a pivotal part in tumour stroma formation. Moreover, macrophages are abundant in areas of tumour cell proliferation, where evidence of macrophage-induced tumour cell killing is rare or absent.[136]

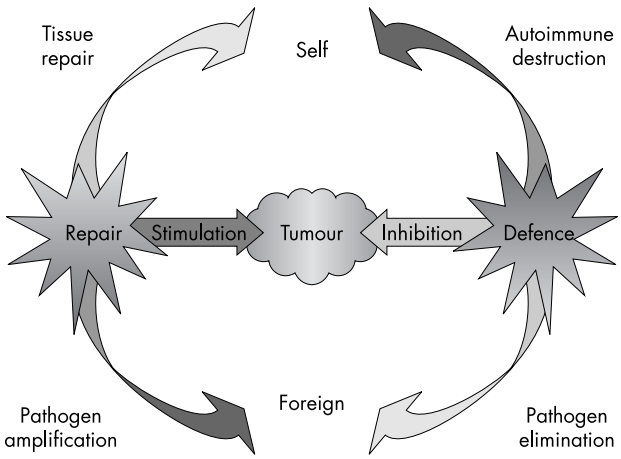

Figure 1 The model illustrates the double edged nature of the immune system. When a tumour develops, the relative balance of these two arms determines its outcome. Tumour induces the reparative arm and thus subverts leucocyte growth-promoting activities to its own benefit. An exogenous antigenic stimulus such as Coley's vaccine may shift the balance back to the defensive arm resulting in tumour regression. Dark grey arrows represent a detrimental and light grey arrows a beneficial immune response.

Coley observed more intense reactions in highly vascular tumours.[15] In these tumours, rapid degeneration occurred, often with the formation of sloughs. He also noted that less vascular tumours, in contrast, more often regressed through slow absorption without breaking down or sloughing. The tortuous and fragile nature of tumour vasculature compared with ordinary vessels[141] makes it more susceptible to febrile immunostimulated collapse, resulting in haemorrhagic necrosis of the dependent tumour mass. The simultaneous suspension of immune reparative functions also counters tumour growth (fig 1).[8] For example, macrophages secrete a wide range of factors, some of which stimulate blood and lymphatic vessel development (for example, platelet-derived growth factor, vascular endothelial growth factor-A, -B, -C, -D).[131 142 143] A shift to the defensive mode downregulates the production of these factors. A final key factor contributing to tumour regression involves the direct killing of tumour cells by macrophages (for example, production of reactive oxygen and nitrogen metabolites). The fact that macrophages express Toll-like receptors involved in both defence and repair underscores the delicate balance that exists between immune-mediated tumour growth and regression. Thus, the presence of hypoxia or necrosis in an otherwise sterile tumour can induce the release of factors that stimulate tumour growth; while the introduction of Coley's vaccine, or other bacterial, viral, or fungal products, can shift the balance back towards a defensive immune response (fig 1).

There is often confusion in the literature as to what constitutes an immune response and what constitutes a side effect. For example, in a review on high dose interferon-α for the treatment of melanoma, it states that flu-like symptoms associated with this therapy ''are quite manageable … with prophylactic antipyretics … to control fever, headache, and myalgia''.[144] Thus, the immune system is stimulated on the one hand with interferon-α, even as it is suppressed on the other with antipyretics. Little consideration is given as to whether these flu-like symptoms can improve patient survival. Although severe adverse effects must be avoided, a failure to recognise aspects of the immune response that are critical to disease regression counters the effectiveness of the treatment. Moreover, single cytokine therapies may result in many unique toxicities due to the fact that such treatments present an unnatural challenge. Although Coley's vaccine and treatment regimen was not free of adverse symptoms, it is crucial to understand that the symptoms arising from this form of treatment (for example, chills, fever, fatigue, etc) are normal adaptive responses to immunostimulation and facilitate disease regression. Furthermore, the beneficial effect of this regimen on cancer pain would have dual advantages—suppression of pain also leads to reduced usage of agents that inhibit key aspects of the immune response, such as antipyretics[145] and opioids.[146 147]

A final point concerns the paradoxical influence of acute and chronic infections on tumour formation. It is now well established that some malignancies arise in association with chronic infections of one type or another. *Helicobacter pylori* and gastric cancer, *Schistosoma haematobium* and bladder cancer, and human papilloma virus and cervical cancer are some examples. These infectious diseases generally afflict the organ where the cancer later develops. However, unlike the acute febrile response, a chronic infection generally represents a failed immune response to disease, and many mechanisms have been uncovered to explain the infectious role in tumour promotion.[148] Yet, even chronic infections may have temporary periods of benefit as during an acute flare-up or concurrent illness.[8 149]

Questions (true/false; answers below)

1. Coley was the first to use live bacteria as an immunotherapy for cancer.
2. Coley's vaccine was only effective when directly injected into the primary tumour.
3. Fever generation increases the metabolic rate to a greater degree than fever maintenance.
4. An infection in a cold blooded animal induces a ''fever'' response.
5. Tumour necrosis factor-α was sole factor responsible for the effects of Coley's vaccine.
6. Immune cells are important for tissue repair during wound healing.
7. Macrophages can induce the formation of both blood and lymphatic vessels.
8. A non-specific immune response to the cancer can play a major part in tumour regression.
9. Chronic infections may be associated with the spontaneous regression of cancer.
10. Coley's vaccine was more effective for the treatment of sarcomas than carcinomas.

Answers

1. False. There are many examples that precede Coley's work.
2. False. Numerous case reports have been published where metastatic lesions regressed without direct injection.
3. True. By analogy, acceleration of an automobile uses more fuel than maintaining its speed at a higher velocity.
4. True. Experimental studies demonstrate that cold blooded animals will preferably move to a warmer microclimate after infection to increase their body temperature. Antipyretics suppress this behaviour.
5. False. As there is not one dietary component responsible for proper nutrition, nor is one cytokine responsible for the effects of Coley's vaccine.
6. True. In vivo and in vitro studies have found that immune cells are capable of phagocytising debris, producing cellular growth factors, and stimulating the formation of new blood and lymphatic vessels.
7. True. Macrophages have been shown to produce both blood and lymphatic-specific growth factors.
8. True. Although specific immunity may be involved in tumour regression, there is evidence from many sources that the non-specific immune response can cause cancer regression.
9. True. Cases of spontaneous cancer regression in patients with chronic infections have been reported; generally, in the initial acute phase of the infection, during an acute flare-up, or during a concurrent illness.
10. False. Although more sarcomas were treated than carcinomas, evidence suggests that survival rates were similar. In fact, bone sarcomas generally showed the poorest survival.

PLACE IN THE FUTURE

The ability of the immune system to provoke ''spontaneous'' regressions has been reduced by use of immunosuppressive therapies such as chemotherapy, radiation and antipyretics, as well as the reduction of infections by sterile surgical techniques and antibiotics. Retrospective studies in lung cancer patients,[50 150 151] however, suggest that there is a significant benefit when such accidental infections occur. More comprehensive studies in cancers where significant postoperative infections are not uncommon (for example, bladder, lung, colorectal) are required.

After being used for almost 70 years and despite hundreds of publications on its effects on cancer, Coley's vaccine was assigned ''new drug'' status in 1963 by the US Food and Drug Administration. This ruling forces anyone interested in this area to go through a considerably expensive series of testing protocols that essentially bar Coley's treatment from being used on cancer patients. After this date, the opportunity to develop an inexpensive and effective vaccine for the treatment of a wide spectrum of cancers was virtually lost.

One way of testing Coley's regimen would be to apply it in spontaneously occurring animal tumours. With recruitment from veterinary practices and in consultation with owners, seemingly hopeless cases could be sought to demonstrate the utility of this approach against metastatic disease. Alternatively, a pilot phase I study in terminal cancer patients may be an option. Key points that Coley considered essential for tumour regression could be investigated: inducing fevers, direct tumour injections, and repeated injections; at the same time, the adverse effects of the vaccine could be quantified. Contributing factors that support the induction and maintenance of fever, which appears to be an essential component for treating metastatic cancer, could be further analysed. In addition, treatment effects could be monitored through the measurement of serum tumour markers, cytokine expression, and immune cell number and activity. Once the principles of Coley's treatment have been re-established and put into perspective in relation to the large amount of human data that are already available, more comprehensive human studies could be undertaken.

A revival of interest and a closer look at the scientific merits of Coley's treatment may seem to some like a doctrine that would make cancer research go backwards; yet judging from the slow progress of conventional cancer treatments, a step backward may indeed be a giant leap forward.

ACKNOWLEDGEMENTS

SAHC is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research.

Authors' affiliations

S A Hoption Cann, C van Netten, Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada
J P van Netten, Special Development Laboratory, Royal Jubilee Hospital and Department of Biology, University of Victoria, Victoria, British Columbia, Canada

REFERENCES

1 **Shaw GB**. *The doctor's dilemma, getting married, and the shewing-up of Blanco Posnet*. London: Constable and Co, 1947:102.
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 **Coley WB**. Contribution to the knowledge of sarcoma. *Ann Surg* 1891;**14**:199–220.
4 **Coley WB**. Treatment of inoperable malignant tumors with toxins of erysipelas and the bacillus prodigiosus. *Trans Am Surg Assn* 1894;**12**:183–212.
5 **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.

6 **Rosenberg S**. *The transformed cell: unlocking the mysteries of cancer*. London: Chapmans, 1985:59.
7 **Thomas-Tikhonenko A**, Hunter CA. Infection and cancer: the common vein. *Cytokine Growth Factor Rev* 2003;**14**:67–77.
8 **Hoption Cann SA**, van Netten JP, van Netten C, *et al*. Spontaneous regression: a hidden treasure buried in time. *Med Hypotheses* 2002;**58**:115–9.
9 **Anonymous**. Erysipelas and prodigiosus toxins (Coley). *JAMA* 1934;**103**:1067–9.
10 **Nauts HC**. *Breast cancer: immunological factors affecting incidence, prognosis and survival*. Monograph No 18. New York: Cancer Research Institute, 1984.
11 **Nauts HC**. *The beneficial effects of bacterial infections on host resistance to cancer: end results in 449 cases*. 2nd Ed. Monograph No 8. New York: Cancer Research Institute, 1980.
12 **Coley WB**. *The treatment of malignant inoperable tumors with the mixed toxins of erysipelas and bacillus prodigiosus with a brief report of 80 cases successfully treated with the toxins from 1893–1914*. Brussels: M Weissenbruch, 1914.
13 **Winberg OK**. Inoperable round-celled sarcoma of the upper jaw with metastases successfully treated with the mixed toxins of erysipelas and bacillus prodigiosus. *Med Rec* 1902;**61**:681–4.
14 **Nauts HC**. Immunotherapy of cancer by microbial products. In: Mizuno D, ed. *Host defense against cancer and its potentiation*. Baltimore, MD: University Park Press, 1975:337–51.
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**:375–430.
16 **Da Costa JC**. *Modern surgery*. 10th Ed. Philadelphia: WB Saunders, 1931:293–4.
17 **Turner GG**. *Modern operative surgery*. 3rd Ed. London: Cassell, 1943;**1**:304.
18 **Starnes CO**. Coley's toxins in perspective. *Nature* 1992;**357**:11–2.
19 **Bickels J**, Kollender Y, Merinsky O, *et al*. Coley's toxin: historical perspective. *Isr Med Assoc J* 2002;**4**:471–2.
20 **Coley WB**. Disappearance of a recurrent carcinoma after injections of mixed toxins. *Ann Surg* 1912;**55**:897–8.
21 **Coley WB**. Inoperable adenocarcinoma of the soft palate, rendered operable by use of the mixed toxins. *Ann Surg* 1913;**58**:559–61.
22 **Coley WB**. Inoperable recurrent tumor of nasopharynx, involving ethmoid, sphenoid, frontal and superior maxillae bones (carcinoma); disappearance under six weeks' treatment with the mixed toxins. *Ann Surg* 1915;**62**:353–8.
23 **Lagueux P**. Le sérum de Coley dans le cas de sarcome ou carcinome ou dans le cas de récedive après opération. *Bull Med Quebec* 1908;**10**:469–70.
24 **Richardson MA**, Ramirez T, Russell NC, *et al*. Coley toxins immunotherapy: a retrospective review. *Altern Ther Health Med* 1999;**5**:42–7.
25 **Pack GT**. St Peregrine, OSM—the patron saint of cancer patients. *CA Cancer J Clin* 1967;**17**:83–84.
26 **Jackson R**. Saint Peregrine, OSM—the patron saint of cancer patients. *CMAJ* 1974;**111**:824–7.
27 **Ebbell B**. *The Papyrus Ebers: the greatest Egyptian medical document*. London: Oxford University Press, 1937.
28 **Tanchou S**. Recherches sur le traitement médical des tumeurs cancéreuses du sein. *Ouvrage practique basé sur trois cents observations (extraits d'un grand nombre d'auteurs)*. Paris: G Baillière, 1844.
29 **Amoureax A**. Sur l'usage intérieur de la belladonna. *J Med Chir Pharm* 1760;**13**:47–65.
30 **Busch W**. Niederrheinische Gesellshaft fur Natur und Heilkunde in Bonn. *Berlin Klin Wochenschr* 1868;**5**:137–8.
31 **Fehleisen F**. On erysipelas. In: Cheyne WW, ed. *Recent essays on bacteria in relation to disease*. London: New Sydenham Society, 1886:263–86.
32 **Cruveilhier J**. *Traité d'anatomie pathologique générale*. Paris: JB Baillière, 1864;**5**:251.
33 **Dussaussoy**. *Dissertations et observations sur la gangrène dans les hôpitaux*. Lyon, 1787.
34 **Robert LMS**. *L'art de prévenir le cancer au sein chez les femmes qui touchent à leur époque critique*. Paris, 1812:155.
35 **Didot A**. Prophylaxie du cancer par la syphilization. *Presse Med* 1852;**4**:117–9, 143–5.
36 **Alquié A**. Inoculation de la syphilis au cancer. *Gaz Hop* 1851;**24**:546.
37 **Lister J**. *The collected papers of Joseph, Baron Lister*. Oxford: Clarendon Press, 1906.
38 **Thiery P**. À propos de la fulguration dans le cancer. *Bull Mem Soc Chir Paris* 1909;**35**:604–98.
39 **Ifrah N**, James JM, Viguie F, *et al*. Spontaneous remission in adult acute leukemia. *Cancer* 1985;**56**:1187–90.
40 **Maekawa T**, Fujii H, Horiike S, *et al*. Spontaneous remission of four months' duration in hypoplastic leukemia with tetraploid chromosome after blood transfusions and infection. *Nippon Ketsueki Gakkai Zasshi* 1989;**52**:849–57.
41 **Sureda M**, Subira ML, Martin Algarra S, *et al*. Spontaneous tumor regression. Report of 2 cases. *Med Clin (Barc)* 1990;**95**:306–8.
42 **Rebollo J**, Llorente I, Yoldi A. Spontaneous tumor regression in a patient with metastatic gastric cancer. Communication of an additional case. *Rev Med Univ Navarra* 1990;**34**:141–2.
43 **Fassas A**, Sakellari I, Anagnostopoulos A, *et al*. Spontaneous remission of acute myeloid leukemia in a patient with concurrent Pneumocystis carinii pneumonia. *Nouv Rev Fr Hematol* 1991;**33**:363–4.
44 **Marcos Sanchez F**, Juarez Ucelay F, Bru Espino IM, *et al*. A new case of spontaneous tumor regression. *An Med Interna* 1991;**8**:468.
45 **Frick S**, Frick P. Spontaneous remission in chronic lymphatic leukemia. *Schweiz Med Wochenschr* 1993;**123**:328–34.
46 **Delmer A**, Heron E, Marie JP, *et al*. Spontaneous remission in acute myeloid leukaemia. *Br J Haematol* 1994;**87**:880–2.
47 **Garcia-Rayo S**, Gurpide A, Vega F, *et al*. Spontaneous tumor regression in a patient with multiple myeloma: report of another case. *Rev Med Univ Navarra* 1996;**40**:41–2.
48 **Mitterbauer M**, Fritzer-Szekeres M, Mitterbauer G, *et al*. Spontaneous remission of acute myeloid leukemia after infection and blood transfusion associated with hypergammaglobulinaemia. *Ann Hematol* 1996;**73**:189–93.
49 **Bowles AP Jr**, Perkias E. Long-term remission of malignant brain tumors after intracranial infection: a report of four cases. *Neurosurgery* 1999;**44**:636–42.
50 **Tzankov A**, Ludescher C, Duba HC, *et al*. Spontaneous remission in a secondary acute myelogenous leukaemia following invasive pulmonary aspergillosis. *Ann Hematol* 2001;**80**:423–5.
51 **Ruckdeschel JC**, Codish SD, Stranahan A, *et al*. Postoperative empyema improves survival in lung cancer: documentation of a natural experiment. *N Engl J Med* 1972;**287**:1013–7.
52 **Nauts HC**, Pelner L, Fowler GA. *Sarcoma of the soft tissues, other than lymphosarcoma, treated by toxin therapy. End results in 186 determinant cases with microscopic confirmation of the diagnosis: 49 operable, 137 inoperable*. Monograph No 3. New York: Cancer Research Institute, 1969.
53 **Isaacs SN**, Axelrod PI, Lorber B. Antipyretic orders in a university hospital. *Am J Med* 1990;**88**:31–5.
54 **Thomas V**, Riegel B, Andrea J, *et al*. National survey of pediatric fever management practices among emergency department nurses. *J Emerg Nurs* 1994;**20**:505–10.
55 **Stites DP**, Terr AI, Parslow TG. *Medical immunology*. Stamford, CT: Appleton and Lange, 1997:680.
56 **Rosenberg HF**, Gallin JI. Inflammation. In: Paul WE, ed. *Fundamental immunology*. 4th Ed. Philadelphia: Lippincott-Raven, 1999:1053.
57 **Roitt IM**, Delves PJ. *Essential immunology*. 10th Ed. Oxford: Blackwell Science, 2001.
58 **Bierman W**. The history of fever therapy in the treatment of disease. *Bull N Y Acad Sci* 1942;**18**:65–75.
59 **Wunderlich CA**. *On the temperature in diseases: a manual of medical thermometry*. 2nd Ed. London: New Sydenham Society, 1871:XLIX.
60 **Bonadio WA**, Romine K, Gyuro J. Relationship of fever magnitude to rate of serious bacterial infections in neonates. *J Pediatr* 1990;**116**:733–5.
61 **Mackowiak PA**, Wasserman SS, Levine MM. An analysis of the quantitative relationship between oral temperature and severity of illness in experimental shigellosis. *J Infect Dis* 1992;**166**:1181–4.
62 **Mackowiak PA**, Wasserman SS, Tacket CO, *et al*. Quantitative relationship between oral temperature and severity of illness following inoculation with candidate attenuated dengue virus vaccines. *Clin Infect Dis* 1994;**19**:948–50.
63 **Bryant RE**, Hood AF, Hood CE, *et al*. Factors affecting mortality of gram-negative rod bacteremia. *Arch Intern Med* 1971;**127**:120–8.
64 **Weinstein MP**, Murphy JR, Reller LB, *et al*. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. *Rev Infect Dis* 1983;**5**:54–70.
65 **Roghmann MC**, Warner J, Mackowiak PA. The relationship between age and fever magnitude. *Am J Med Sci* 2001;**322**:68–70.
66 **Whitrow M**. Wagner-Jauregg and fever therapy. *Med Hist* 1990;**34**:294–310.
67 **Wagner-Jauregg J**. Ueber die Einwirkung fieberhafter Erkrankungen auf Psychosen. *Jb Psychiat Neurol* 1887;**7**:94–131.
68 **Wagner-Jauregg J**. *Fieber und Infektionstherapie*. Wien: Weidmann, 1936:115–6.
69 **Moore JE**. *The modern treatment of syphilis*. 2nd Ed. Springfield, IL: CC Thomas, 1941.
70 **O'Leary PA**. Treatment of neurosyphilis by malaria: report of the three years observation of the first one hundred patients treated. *JAMA* 1927;**89**:95–100.
71 **Krauss W**. Analysis of reports of 8354 cases of IMPF-malaria. *South Med J* 1932;**25**:537–41.
72 **Bond P**. *General paralysis and its treatment by induced malaria*. London: HM Stationery Office, 1929.
73 **Chernin E**. The malariatherapy of neurosyphilis. *J Parasitol* 1984;**70**:611–7.
74 **Wagner-Jauregg J**. Psychiatrische Heilbestrebungen. *Wein Klin Wschr* 1895;**8**:155–9.
75 **Falk MH**, Issels RD. Hyperthermia in oncology. *Int J Hyperthermia* 2001;**17**:1–18.
76 **Aubert A**. Sickness and behaviour in animals: a motivational perspective. *Neurosci Biobehav Rev* 1999;**23**:1029–36.
77 **Hasday JD**, Fairchild KD, Shanholtz C. The role of fever in the infected host. *Microbes Infect* 2000;**2**:1891–904.
78 **Baracos VE**, Whitmore WT, Gale R. The metabolic cost of fever. *Can J Physiol Pharmacol* 1987;**65**:1248–54.
79 **Hart BL**. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* 1988;**12**:123–37.
80 **Kluger MJ**. *Fever: its biology, evolution, and function*. Princeton, NJ: Princeton University Press, 1979.
81 **Kluger MJ**. The adaptive value of fever. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. New York: Raven Press, 1991:105–24.

82 **Toms GL**, Davies JA, Woodward CG, *et al*. The relation of pyrexia and nasal inflammatory response to virus levels in nasal washings of ferrets infected with influenza viruses of differing virulence. *Br J Exp Pathol* 1977;**58**:444–58.
83 **Vaughn LK**, Veale WL, Cooper KE. Antipyresis: its effect on mortality rate of bacterially infected rabbits. *Brain Res Bull* 1980;**5**:69–73.
84 **Vaughn LK**, Veale WL, Cooper KE. Effects of antipyresis on bacterial numbers in infected rabbits. *Brain Res Bull* 1981;**7**:175–80.
85 **Husseini RH**, Sweet C, Collie MH, *et al*. Elevation of nasal viral levels by suppression of fever in ferrets infected with influenza viruses of differing virulence. *J Infect Dis* 1982;**145**:520–4.
86 **Dwinger RH**, Vos J, Nieuwenhuijs J, *et al*. Studies on the influence of non-steroidal anti-inflammatory drugs upon trypanosomiasis in goats and sheep. *J Vet Pharmacol Ther* 1984;**7**:293–301.
87 **Esposito AL**. Aspirin impairs antibacterial mechanisms in experimental pneumococcal pneumonia. *Am Rev Respir Dis* 1984;**130**:857–62.
88 **Kurosawa S**, Kobune F, Okuyama K, *et al*. Effects of antipyretics in rinderpest virus infection in rabbits. *J Infect Dis* 1987;**155**:991–7.
89 **Crocker JF**, Digout SC, Lee SH, *et al*. Effects of antipyretics on mortality due to influenza B virus in a mouse model of Reye's syndrome. *Clin Invest Med* 1998;**21**:192–202.
90 **Dianzani F**, Baron S. Nonspecific defenses. In: Baron S, ed. *Medical microbiology*. Menlo Park, CA: Addison-Wesley, 1982:562–3.
91 **Brandts CH**, Ndjave M, Graninger W, *et al*. Effect of paracetamol on parasitic clearance time in Plasmodium falciparum malaria. *Lancet* 1997;**350**:704–9.
92 **Doran TF**, DeAngelis C, Baumgardner RA, *et al*. Acetominophen: more harm than good for chickenpox? *J Pediatr* 1989;**114**:1045–8.
93 **Sugimura T**, Fujimoto T, Motoyama H, *et al*. Risks of antipyretics in young children with fever due to infectious disease. *Acta Paediatr Jpn* 1994;**36**:375–8.
94 **Graham NM**, Burrell CJ, Douglas RM, *et al*. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis* 1990;**162**:1277–82.
95 **Stanley ED**, Jackson GG, Parusam C, *et al*. Increased viral shedding with aspirin treatment of rhinovirus infection. *JAMA* 1975;**231**:1248–51.
96 **Plaisance KI**, Kudaravalli S, Wasserman SS, *et al*. Effect of antipyretic therapy on the duration of illness in experimental influenza A, Shigella sonnei, and Rickettsia rickettsii infections. *Pharmacotherapy* 2000;**20**:1417–22.
97 **Rietveld JA**, Pilmore HL, Jones PG, *et al*. Necrotising fasciitis: a single centre's experience. *N Z Med J* 1995;**108**:72–4.
98 **Zerr DM**, Alexander ER, Duchin JS, *et al*. A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999;**103**:783–90.
99 **Barnham MR**, Weightman NC, Anderson AW, *et al*. Streptococcal toxic shock syndrome: a description of 14 cases from North Yorkshire, UK. *Clin Microbiol Infect* 2002;**8**:174–81.
100 **Byington CL**, Spencer LY, Johnson TA, *et al*. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. *Clin Infect Dis* 2002;**34**:434–40.
101 **Quesnay F**. *Traité de la gangrène*. Paris: d'Houry, 1749:313.
102 **Broca PP**. *Traité des tumeurs*. Paris: P Asselin, 1866;**1**:240–62.
103 **Verneuil A**. De l'inoculation de l'érysipèle comme moyen curatif. *Union Med (Paris)* 1886;**41**:19–22, 217–21.
104 **Mohr C**. A case of carcinoma of the breast vs erysipelas and arsenic. *North Am J Homeop* 1888;**3**:700–2.
105 **Celsus AC**. *De Medicina*. Spencer WG, ed. London: W Heinemann, 1938;**1**:273.
106 **Shear MJ**, Turner FC. Chemical treatment of tumors; isolation of hemorrhagic-producing fraction from Serratia marcescens (Bacillus prodigiosus) culture filtrate. *J Natl Cancer Inst* 1943;**4**:81–7.
107 **Algire GH**, Legallais FY, Park HD. Vascular reactions of normal and malignant tissues in vivo. II. The vascular reaction of normal and neoplastic tissues of mice to a bacterial polysaccharide from Serratia marcescens (Bacillus prodigiosus) culture filtrates. *J Natl Cancer Inst* 1947;**8**:53–62.
108 **Old LJ**. Tumor necrosis factor. *Sci Am* 1988;**258**:59–60, 69–75.
109 **Nethersell AB**. Biological modifiers and their role in cancer therapy. *Ann Acad Med Singapore* 1990;**19**:223–34.
110 **Oettgen HF**. Biological agents in cancer therapy: cytokines, monoclonal antibodies and vaccines. *J Cancer Res Clin Oncol* 1990;**116**:116–9.
111 **Bassi P**. BCG (bacillus of Calmette Guerin) therapy of high-risk superficial bladder cancer. *Surg Oncol* 2002;**11**:77–83.
112 **Viallard JF**, Denis D, Texier-Maugein J, *et al*. Disseminated infection after bacille Calmette-Guerin instillation for treatment of bladder carcinoma. *Clin Infect Dis* 1999;**29**:451–2.
113 **Gottke MU**, Wong P, Muhn C, *et al*. Hepatitis in disseminated bacillus Calmette-Guerin infection. *Can J Gastroenterol* 2000;**14**:333–6.
114 **Bohle A**, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;**169**:90–5.
115 **Fleischmann JD**, Toossi Z, Ellner JJ, *et al*. Urinary interleukins in patients receiving intravesical Bacillus Calmette-Guerin therapy for superficial bladder cancer. *Cancer* 1989;**64**:1447–54.
116 **Bohle A**, Nowc C, Ulmer AJ, *et al*. Elevations of cytokines interleukin-1, interleukin-2 and tumor necrosis factor in the urine of patients after intravesical bacillus Calmette-Guerin immunotherapy. *J Urol* 1990;**144**:59–64.
117 **de Boer EC**, Somogyi L, de Ruiter GJ, *et al*. Role of interleukin-8 in onset of the immune response in intravesical BCG therapy for superficial bladder cancer. *Urol Res* 1997;**25**:31–4.
118 **Poppas DP**, Pavlovich CP, Folkman J, *et al*. Intravesical bacille Calmette-Guerin induces the antiangiogenic chemokine interferon-inducible protein 10. *Urology* 1998;**52**:268–75.
119 **Taniguchi K**, Koga S, Nishikido M, *et al*. Systemic immune response after intravesical instillation of bacille Calmette-Guerin (BCG) for superficial bladder cancer. *Clin Exp Immunol* 1999;**115**:131–5.
120 **Thalmann GN**, Sermier A, Rentsch C, *et al*. Urinary interleukin-8 and 18 predict the response of superficial bladder cancer to intravesical therapy with bacillus Calmette-Guerin. *J Urol* 2000;**164**:2129–33.
121 **Watanabe E**, Matsuyama H, Matsuda K, *et al*. Urinary interleukin-2 may predict clinical outcome of intravesical bacillus Calmette-Guerin immunotherapy for carcinoma in situ of the bladder. *Cancer Immunol Immunother* 2003;**52**:481–6.
122 **Rohdenburg GL**. Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. *J Cancer Res* 1918;**3**:193–225.
123 **Lucey DR**, Clerici M, Shearer GM. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. *Clin Microbiol Rev* 1996;**9**:532–62.
124 **Molinari JA**, Carrick L Jr, Lubiniecki AS. Influence of Trichinella spiralis infection on development of sarcoma-180 ascites tumors. *Tropenmed Parasitol* 1979;**30**:429–33.
125 **Cabral HR**. The tumoricidal effect of Trypanosoma cruzi: its intracellular cycle and the immune response of the host. *Med Hypotheses* 2000;**54**:1–6.
126 **Medzhitov R**. Toll-like receptors and innate immunity. *Nat Rev Immunol* 2001;**1**:135–45.
127 **Okamoto M**, Sato M. Toll-like receptor signaling in anti-cancer immunity. *J Med Invest* 2003;**50**:9–24.
128 **van Netten JP**, Ashmed BJ, Cavers D, *et al*. ''Macrophages'' and their putative significance in human breast cancer. *Br J Cancer* 1992;**66**:220–1.
129 **van Netten JP**, George EJ, Ashmead BJ, *et al*. Macrophage-tumour cell associations in breast cancer. *Lancet* 1993;**342**:872–3.
130 **al-Sarireh B**, Eremin O. Tumour-associated macrophages (TAMS): disordered function, immune suppression and progressive tumour growth. *J R Coll Surg Edinb* 2000;**45**:1–16.
131 **Schoppmann SF**, Birner P, Stockl J, *et al*. Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. *Am J Pathol* 2002;**161**:947–56.
132 **van Netten JP**, Ashmead BJ, Parker RL, *et al*. Macrophage-tumor cell associations: a factor in metastasis of breast cancer? *J Leukoc Biol* 1993;**54**:360–2.
133 **Oleszczuk JJ**, van Netten JP, Ross AS. Biological aspects of breast cancer metastasis: consequences of tumor cell/macrophage interactions. *Klin Perinatol Ginecol* 1994;**12**:215–21.
134 **Whalen GF**. Solid tumours and wounds: transformed cells misunderstood as injured tissue? *Lancet* 1990;**336**:1489–92.
135 **van Netten JP**, Mogentale T, Smith MJ, *et al*. Physical trauma and breast cancer. *Lancet* 1994;**343**:978–9, 1365–6.
136 **Hoption Cann SA**. The immune system and breast carcinoma: implications of dietary and other associated factors. PhD Dissertation. Victoria, BC: University of Victoria, 2001.
137 **Gordon S**. Macrophages and the immune response. In: Paul WE, ed. *Fundamental immunology*. 4th Ed. Philadelphia: Lippincott-Raven, 1999:533–46.
138 **Schmeisser A**, Garlichs CD, Zhang H, *et al*. Monocytes coexpress endothelial and macrophagocytic lineage markers and form cord-like structures in Matrigel under angiogenic conditions. *Cardiovasc Res* 2001;**49**:671–80.
139 **Rehman J**, Li J, Orschell CM, *et al*. Peripheral blood ''endothelial progenitor cells'' are derived from monocyte/macrophages and secrete angiogenic growth factors. *Circulation* 2003;**107**:1164–9.
140 **Adams EF**, Newton CJ, Braunsberg H, *et al*. Effects of human breast fibroblasts on growth and 17 beta-estradiol dehydrogenase activity of MCF-7 cells in culture. *Breast Cancer Res Treat* 1988;**11**:165–72.
141 **Hashizume H**, Baluk P, Morikawa S, *et al*. Openings between defective endothelial cells explain tumor vessel leakiness. *Am J Pathol* 2000;**156**:1363–80.
142 **Barbera-Guillem E**, Nyhus JK, Wolford CC, *et al*. Vascular endothelial growth factor secretion by tumor-infiltrating macrophages essentially supports tumor angiogenesis, and IgG immune complexes potentiate the process. *Cancer Res* 2002 1;**62**:7042–9.
143 **Kataki A**, Scheid P, Piet M, *et al*. Tumor infiltrating lymphocytes and macrophages have a potential dual role in lung cancer by supporting both host-defense and tumor progression. *J Lab Clin Med* 2002;**140**:320–8.
144 **Kirkwood JM**, Bender C, Agarwala S, *et al*. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002;**20**:3703–18.
145 **Kluger MJ**, Kozak W, Conn CA, *et al*. Role of fever in disease. *Ann N Y Acad Sci* 1998;**856**:224–33.
146 **Mayfield KP**, Kozak A, Rudolph K, *et al*. Morphine suppresses development of fever to lipopolysaccharide in rats. *Ann N Y Acad Sci* 1998;**856**:281–5.
147 **Wei G**, Moss J, Yuan CS. Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? *Biochem Pharmacol* 2003;**65**:1761–6.
148 **Lax AJ**, Thomas W. How bacteria could cause cancer: one step at a time. *Trends Microbiol* 2002;**10**:293–9.

149 **Honkoop AH**, Kaan JA, van de Stadt J, *et al*. A man with spontaneous regression of non-Hodgkin lymphoma, hypergammaglobulinemia and infection caused by 2 herpesviruses; causality or coincidence? *Ned Tijdschr Geneeskd* 1993;**137**:774–7.
150 **Sensenig DM**, Rossi NP, Ehrenhaft JL. Results of the surgical treatment of bronchogenic carcinoma. *Surg Gynecol Obstet* 1963;**116**:279–84.
151 **Takita H**. Effect of postoperative empyema on survival of patients with bronchogenic carcinoma. *J Thorac Cardiovasc Surg* 1970;**59**:642–4.