7.3.1 Spontaneous tumor disappearance

> *That cancer cells are often sick cells and die young is known to every pathologist.*
>
> (Rous and Kidd 1941)

One of the most stubborn misconceptions is that cancer cells are rapidly dividing super cells, "the enemy within" that is bent on our destruction (Nowell et al. 1998). Hence the military metaphors and the "war on cancer". However, observationally, experimentally, and theoretically, cancer cells are aneuploid cells (Chapters 5 & 6). Aneuploidy damages cells—the more severe the chromosomal imbalance, the greater the damage (Lindsley et al. 1972, Liu et al. 1998). Being damaged, aneuploid cells typically divide at slower rates than normal diploid cells (Hayflick 1965) and "progression does not necessarily lead to dominance of the tumor over its host" (Foulds 1954). Being damaged, aneuploid cells tend to die at high rates (Steel and Lamerton 1969), one of the "liabilities of the neoplastic state" (Rous and Kidd 1941). It is only the "successful" tumors that attract attention; the "unsuccessful" ones escape notice (Foulds 1954). Herein lies the key to prevention and much more effective and less toxic therapeutic approaches to cancer.

Cancer cells are not super cells but damaged aneuploid cells, which for the most part spontaneously die. Since aneuploid cells typically lose in competition with normal diploid cells (Atkin and Baker 1990, Rous and Kidd 1941), the new strategy is to stop devising poisons to kill cancer cells and to focus more on the interactions between tumor and host. The fact that propagation of primary human cancer cells *in vitro* requires finally-tuned, stable environments (see *Cancer research would benefit from de-emphasizing cell culture*, p. 196) implies that non-toxic perturbations of the host may be sufficient to nudge the tumor out of its stable, comfortable environment into a different attractor that leads to the death of the cancer cells.

As Upender et al. said, "[T]he normalization of the complex dysregulation of transcriptional activity in carcinomas requires a more general, less specific, and hence more complex interference" (Upender et al. 2004). Chromosomal imbalance theory demonstrates

that in order to alter a complex phenotype non-toxically requires only moderate changes in the activities of hundreds or even thousands of genes and their products (Section 5.4). While changes in the activities of large numbers of genes merely exercise normal cells, the resulting physical and metabolic perturbations stress and destabilize cancer cells, reducing or terminating their viability within the host (Niakan 1998, Pettigrew et al. 1974, Rous and Kidd 1941). Such perturbations may be responsible for the 741 documented examples of spontaneous remission from more than 45 different types of cancer (Challis and Stam 1990, Kleef et al. 2001). (Some advocate using the term "remission" for permanent disappearance of cancer and "regression" for temporary or partial improvement. In practice, however, spontaneous regression and remission are commonly used as synonyms for unexpected transient or final improvements in cancer.)

The most striking feature of virtually all cases of spontaneous remission was a prior fever-inducing infection: diphtheria, gonorrhea, hepatitis, influenza, malaria, measles, smallpox, syphilis and tuberculosis, as well as various other pyogenic and non-pyogenic infections (Nauts 1980). The Remission Project of the Institute of Noetic Sciences surveyed the literature and found the common factor in all the infections associated with spontaneous regression was high fever, usually 40°C for 3–5 days (O'Regan and Hirschberg 1993). It should be noted that these infections do not always produce fevers that high or for that long. Less common global perturbations associated with spontaneous remission are pregnancy, severe dietary changes, and operative trauma with subsequent infection (Challis and Stam 1990, Hoption Cann et al. 2003). There are also the cases of spontaneous remission that seem to happen for no apparent reason (Kappauf et al. 1997), perhaps because as Rous and Kidd have observed, many neoplasms "require continual aid for their survival" (Rous and Kidd 1941) and without it they perish.

It is generally accepted that spontaneous remission is a natural phenomenon whose causes remain unknown at the present. Only when we begin to address the most basic questions can we start to determine the epidemiology of remission. The Medline database

shows between 1966–1992, the terms "spontaneous remission" or "spontaneous regression" appeared 10,603 times as a descriptor and 718 times in titles (O'Regan and Hirschberg 1993). Of these 718 papers, more than 80% of them have appeared in the period 1975–1992 and over 40% appeared during 1985–1992. There have been literally no comprehensive reviews of spontaneous remission of diseases other than cancer (O'Regan and Hirschberg 1993).

One way to determine an overall epidemiology of remission would be to establish a National Remission Registry modeled after the National Tumor Registry. In that way, information on spontaneous remission could be collected and cases of remission tracked in a systematic manner. The building of such an epidemiology could lead to increased understanding of cancer and treatment and the ability to advise patients more precisely regarding prevention and outcome.

Spontaneous remission probably has more to do with changes in the person than changes in the tumor. The former emphasis on controlling and preventing cancer through diet, exercise, avoidance of carcinogens and similar nontoxic strategies needs to be revived and vigorously investigated. The more remission is recognized as legitimate and the more it is understood, the more likely it is we can understand how to stimulate the natural self-repair capacities that exist in everyone to some degree.

7.3.2 Induction of fever as cancer treatment

> *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.*
>
> (Hoption Cann et al. 2003)

The treatment of cancer by injection of bacterial products is based on the fact that for over two hundred years neoplasms have

been observed to regress following acute infections, principally streptococcal (Nauts et al. 1953) (Section 7.3.1). If these cases were not too far-advanced and the infections were of sufficient severity or duration, the tumors completely disappeared and the patients remained free from recurrence. If the infections were mild, or of brief duration, and the neoplasms were extensive or of histological types which were less sensitive to infections or their toxins, only partial or temporary regressions occurred. The first known observation of this phenomenon was published in 1866 by Wilhelm Busch (Busch 1866). But it was William Coley, Chief of the Bone Service at Memorial Hospital in New York, who is best remembered for devoting a lifetime to the subject. He had an international reputation and was an honorary fellow of the Royal College of Surgeons in London.

Prompted in 1891 by the loss of one of his first patients to a sarcoma on her arm, Coley searched for information that might help him treat other patients with similar conditions. This led him to study all cases of sarcoma treated in a New York Hospital during the preceding 15 years (Hoption Cann et al. 2002). His interest in the possible therapeutic value of infections or their toxins was aroused by the strange case of Fred K. Stein. Five operations on Stein's sarcoma of the cheek had failed to control the disease. However, according to hospital records, he recovered completely after two attacks of erysipelas (an acute, sometimes recurrent disease caused by a bacterial infection). Stein was released from the hospital in 1885. In 1892, after a long search, Coley finally located Stein who agreed to be examined and was found to be still free of cancer 7 years after leaving the hospital (Hall 1997).

Coley immediately attempted to produce erysipelas in a patient with twice-recurrent inoperable myxosarcoma of the tonsil and neck. After repeated trials, using four different bacterial cultures, he succeeded. The resulting severe erysipelas caused a spectacular regression of the tumors, leaving only the scar tissue from the former operations (Coley 1906). This patient lived well for 8 more years, but eventually died from a local recurrence.

After attempting to induce erysipelas in 12 other patients, Coley recognized the difficulties—eight were successfully infected through live bacteria and developed a tumor response (two complete remissions), but two died of erysipelas—leading Coley to abandon the use of living cultures. Starting 1893, he settled on a mixture of two heat-killed bacteria, *Streptococcus pyogenes* and *Serratia marcescens*, that successfully induced remission in a number of cancer patients (Hobohm 2009). This mixture became known as Coley's toxins, or Mixed Bacterial Toxins as it is now called.

There were many strong supporters of Coley's toxins, even among the highest levels of the medical establishment, including the Mayo brothers, Joseph Lister and Henri Matagne (Coley 1936, Matagne 1953). But he also had notable opponents. One of the best known was James Ewing, chief pathologist at the New York Hospital where Coley worked. Ewing became famous for describing the sarcoma that would soon to be named after him (Ewing's Sarcoma). The fact that Coley claimed some of his best results in Ewing's sarcoma may have softened Ewing's opposition (Coley 1910), because he acknowledged in his internationally famous textbook *Neoplastic Diseases* that, "In some recoveries from endothelioma of the bone, there is substantial evidence that [Coley] toxins played an essential part" (Ewing 1941).

William Coley's daughter, Helen Coley Nauts, organized and published all of her father's collected papers. In 1997, she won the National Institute of Social Sciences' Gold Medal for Distinguished Service to Humanity. In collaboration with George Fowler and Louis Pelner, she wrote 18 monographs on different cancers treated with Coley Toxins by her father and his contemporaries, including Sarcoma (Nauts 1969), Colorectal Cancer (Fowler 1969b), Melanoma (Fowler 1969a), and Neuroblastoma (Fowler and Nauts 1969). In all, they reported around 2000 cases, of these, 896 were microscopically confirmed. The overall 5-year survival was 51% in operable cases and 46% in inoperable ones (Nauts 1982). For example, in 104 cases of soft tissue sarcomas, 50% of those injected with the toxins lived 5–20 years (O'Regan and Hirschberg 1993).

While tumor regression was often noted within hours of injection with Coley's toxins (Nauts et al. 1953), primary adaptive immune responses were often delayed by several days to a week (Medzhitov 2001). In fact, Coley's experience (Nauts et al. 1953) and an exploratory evaluation of case reports of spontaneous regression (Hoption Cann et al. 2002, Nauts 1980), support the concept that infection-stimulated tumor regression generally results from a "non-specific" innate immune response (Hoption Cann et al. 2003).

In cases where the regression was partial and the acute or febrile phase of the infection subsided, residual tumor generally re-grew (Nauts 1980). Similarly, if the infection recurred or was reintroduced, tumor regression proceeded as before (Nauts 1980). 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 re-growth of residual tumor (Coley 1906)—again suggesting that specific anti-tumor immunity was not a primary mechanism of this vaccine. The broad diversity of organisms capable of eliciting spontaneous regression coupled with its speed are consistent with the observed general, non-specific disruption of the chromosomally unbalanced and metabolically damaged cancer cells.

One unexpected observation by Coley of no small importance was the salutary effect of fever on cancer pain (Nauts et al. 1953). This beneficial property had been observed by others in association with infection-induced tumor regression (Hoption Cann et al. 2003). In fact, patients would often reduce or discontinue their use of narcotic pain medications while receiving treatment. This phenomenon appears to be independent of tumor regression, as it often occurred immediately after toxin injection, preceding such regressions. Lagueux, after many years of experience using Coley's toxins, commented that, "pain always disappeared after the first injections" (Nauts et al. 1953). Actually, this remarkable analgesic effect had 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" (Hoption Cann et al. 2003).

Researchers in the 1960s and 1970s saw things differently. They believed Coley's toxin worked by stimulating the patient's immune system to defeat cancer. It was proposed that specific cell mediated (type 1) or humoral (type 2) immune responses were the key mediators of cancer regression. This led eventually to the discovery of small cell-signaling proteins called cytokines as the cancer-fighting agents of the immune system. However, the cytokines did not turn out to be very effective against cancer in spite of considerable efforts to commercialize them for that purpose (Hoption Cann et al. 2003).

Apparently, the simple fact of elevating temperature was not seriously considered for its anti-cancer effects. This is unfortunate since it is known that slightly elevated temperature causes general non-specific disruption that is damaging to aneuploid cells (Torres et al. 2007). It is also known that high temperature (>39°C) kills cancer cells both *in vivo* and *in vitro*, in a temperature and time dependent manner (the higher the temperature and the longer the exposure, the higher the number of killed cells) (Keech and Wills 1979, Mackey et al. 1992, Pettigrew et al. 1974). Indeed, Coley's toxins produced violent febrile reactions, which he duly noted was the symptom most associated with tumor regression. The fevers he induced usually did not last more than 24 to 48 hours. However, it would seem from subsequent data that a temperature of at least 40°C maintained for 48 to 96 hours is more likely to produce remission than lower temperatures for shorter duration. A retrospective study of patients with inoperable soft tissue sarcomas treated with Coley's toxins found a superior 5-year survival in patients whose fevers averaged 38–40°C, compared with those having little or no fever (<38°C) during treatment (60% v 20%) (Hoption Cann et al. 2003).

Unfortunately, with the 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 (Edwards et al. 2001, Isaacs et al. 1990, Thomas et al. 1994). Many modern immunology texts make little mention of fever, e.g., (Delves et al. 2006), and may disregard it as being "insignificant" (Parslow et al. 2001) or refer to it as a "mystery" (Rosenberg and Gallin 1999).

As Hoption Cann said, "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" (Hoption Cann et al. 2003). Four medical advances have systemically eroded Coley's fever-inducing therapy for cancer:

1. Cancer surgery, like any other operation, became a sterile procedure after acceptance of Lister's aseptic techniques in the late 1800s (Lister 1906). In fact, in a 1909 discussion paper on cancer treatment, one surgeon suggested that the postoperative infections that were common in the past improved survival and should be encouraged (Thiery 1909). Yet in this new era, his suggestion was harshly criticized as "a doctrine that would make surgery go backwards".
2. 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 standardized than Coley's approach and the hope that these therapies would eventually lead to a cure for cancer was high. Such therapies, however, ran counter to Coley's "immunotherapy", as they are highly immunosuppressive.
3. Following World War II, antibiotic use during and after surgery became commonplace. Thus, post-surgical infection rates were reduced even further, in addition to diminishing the severity and duration of those infections that did occur.
4. 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 (Bowles and Perkins 1999, Delmer et al. 1994, Fassas et al. 1991, Frick and Frick 1993, Garcia-Rayo et al. 1996, Ifrah et al. 1985, Maekawa et al. 1989, Marcos Sanchez et al. 1991, Mitterbauer et al. 1996, Rebollo et al. 1990, Ruckdeschel et al. 1972, Sureda et al. 1990, Tzankov et al. 2001) (Section 7.3.1). Table 7.3 summarizes the literature on spontaneous remission of neoplastic diseases associated with infection and/or fever.

Table 7.3 Selected references supporting infection and/or fever in association with spontaneous remission of neoplastic diseases.*

Cancer	*Source*
Bone	(Callan et al. 1975, Cole and Ferguson 1959, Copeland et al. 1985, Eisenbud et al. 1987, Levin 1957)
Brain	(Kapp 1983, Margolis and West 1967)
Breast	(Larsen and Rose 1999)
Burkitt's lymphoma	(Bluming and Ziegler 1971, Ziegler 1976)
Colorectal	(Fucini et al. 1985, Nowacki and Szymendera 1983)
Gastric	(Rebollo et al. 1990, Zambrana Garcia et al. 1996)
Gynecological	(Friedrich 1972)
Head and neck	(Temesrekasi 1969, Woods 1975)
Leukemia (AML, ALL, CML, CLL)	(Barton and Conrad 1979, Bassen and Kohn 1952, Burgess and de Gruchy 1969, Jono et al. 1994, Kizaki et al. 1988, Lefrere et al. 1994, Maekawa et al. 1989, Matzker and Steinberg 1976, Treon and Broitman 1992, Vladimirskaia 1962, Wiernik 1976, Wyszkowski et al. 1969, Zhu and Qian 1986)
Liver	(Chien et al. 1992, Grossmann et al. 1995, Markovic et al. 1996, Tarazov 1996)
Lung	(Greentree 1973, Marcos Sanchez et al. 1991, Mentzer 1995, Ruckdeschel et al. 1972, Takita 1970)

Table 7.3 Contd. ...

Table 7.3 Contd. ...

Lymphoma & Non-Hodgkin	(De Berker et al. 1996, Drobyski and Qazi 1989, Gattiker et al. 1980, Grem et al. 1986, Rao et al. 1995, Sawada et al. 1994, Sureda et al. 1990, Wolf 1989, Zygiert 1971)
Melanoma	(Cook 1992, Grafton 1994, Gunale and Tucker 1975, Motofei 1996, Wagner and Nathanson 1986, Wormald and Harper 1983)
Multiple myeloma	(London 1955)
Prostate	(Katz and Schapira 1982, Schurmans et al. 1996)
Kidney	(Edwards et al. 1996, Mangiapan et al. 1994)
Retinoblastoma	(Hunter 1968, Jain and Singh 1968, Verhoeff 1966)
Sarcoma	(Berner and Laub 1965, Lei et al. 1997, Penner 1953, Weintraub 1969)

*Adapted from Table 1 on page 58 of (Kleef et al. 2001). AML, Acute Myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia; CML, Chronic Myeloid Leukemia; CLL, Chronic Lymphoblastic Leukemia.

A small sign things may be changing is a 2011 report funded by the National Cancer Institute. Huang et al. published the first study to examine the relationship between severity of menopausal symptoms and breast cancer risk among postmenopausal women (Huang et al. 2011). The authors observed that, "increasing intensity of hot flushes was associated with progressively lower risks of all 3 histologic subtypes of breast cancer studied. In particular, women who experienced severe hot flushes with awakening had lower risks of breast cancer compared with women who experienced menopausal symptoms other than hot flushes with awakening and also compared with women who had hot flushes without perspiration." Unfortunately, the authors considered hot flashes as merely "a surrogate marker for hormonal changes that are relevant to the etiology of breast cancer." Hopefully, follow-up studies will investigate the intrinsic importance of hot flashes in warding off cancer.

Hyperthermia

A 2001 report sponsored by the Office of Alternative Medicine at the National Institutes of Health in Bethesda concluded

that, "Pyrogenic substances and the recent use of whole-body hyperthermia to mimic the physiologic response to fever have been successfully administered in palliative and curative treatment protocols for metastatic cancer. Further research in this area is warranted" (Kleef et al. 2001).

The National Cancer Institute's website says: "Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 45°C). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues (van der Zee 2002). By killing cancer cells and damaging proteins and structures within cells (Hildebrandt et al. 2002), hyperthermia may shrink tumors. Hyperthermia is under study in clinical trials (research studies with people) and is not widely available." (http://www.cancer.gov/cancertopics/factsheet/Therapy/hyperthermia)

There are several kinds of hyperthermia treatments: local, regional and whole body. Whole body hyperthermia is being used to treat cancer but unfortunately only in combination with radiation and chemotherapy (van der Zee 2002, Wust et al. 2002). Nevertheless, hyperthermia treatments are becoming more and more common and available in the US, while Germany is leading the use of this promising therapy.

The therapeutic benefit due to elevated temperature is understandable in light of the theory of chromosomal imbalance. As we have seen, aneuploid cells are particularly temperature sensitive to elevated temperatures that are harmless to normal human cells (Keech and Wills 1979, Mackey et al. 1992, Torres et al. 2007). This can be explained (at least in part) by the abnormal metabolism of cancer cells (e.g. the Warburg effect, Section 6.3) caused by aneuploidy. When the temperature raises, there is an increase in the entropy of the cancer cells, which were already at the maximum level of disorganization consistent with viability (Section 6.2.3), leading to rapid and substantial tumor regression.