

## Remarkable Recoveries: Research and Practice from a Patient's Perspective

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**T**wenty-some years ago I was diagnosed with papillary carcinoma of the thyroid. The standard treatment—the removal of the gland and its replacement by a daily pharmaceutical—struck me at the time as radical and alarming. Before agreeing to the procedure, I asked my surgeon if such tumors were ever known to regress.

“Never,” he said, enumerating the mortal dangers of wishful thinking and blind hope. Clearly he found me naïve, and I was—about the sinister depredations of cancer, surely, but also about the degree of (understandable) medical skepticism about the body's self-healing capacity when it comes to cancer's dire domain.

At the time, I was editing a magazine that covered the nascent stirrings of complementary and alternative medicine. I had seen instances where serious disease had resolved in ways that seemed outside the conventional medical paradigm. I noted that such patients had often adopted rigorous alternative regimens, pursued disciplines of mind and body, and made other life-changes to which they (if not their doctors) ascribed their cures.

Their methods usually had no trial-verified therapeutic value (suggesting their conditions were either misdiagnosed, self-resolving, or the result of nonreplicable healing modalities). Nonetheless, I had set out into the unknown, using such crude maps as I could find. I began eating fresh vegetables and whole grains, eliminating red meat, fried foods, refined sugar, and excess salt. Office overtime also went by the wayside. I started on a regimen of yoga and meditation, gulped vitamin supplements, and focused on people and pursuits that made me happy.

Despite my illness, I began to feel better than I had in years. But after several months of this, feeling like a pioneer forging too deep into uncharted territory,

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I opted for a thyroidectomy. I was startled, however, by my postoperative biopsy report: during those months, the volume of the tumor had shrunk by nearly half from its original scanned measurement.

This is not to claim that my ad hoc approach would have effected a cure. The occurrence of so-called “spontaneous remission” of cancer is rare, with estimates ranging from 1 in 60,000 to 1 in 100,000 (though some investigators maintain it is grossly underreported) [1]. Still, my experience led me to spend nearly a decade studying unusual survivors, wondering if the stories of such “outliers” might contain key insights into the healing process.

It is a path trodden by investigators with better credentials. When Dr. Steven Rosenberg, the former Chief of Surgery of the National Cancer Institute (NCI), was a junior surgical resident, he treated a 51-year-old war veteran, one Mr. DeAngelo, for an infected gall bladder. Yet Mr. DeAngelo, with what Rosenberg would later remember as “an aura of secret triumph,” regaled him with a story the young doctor assumed was a product of the befuddlements of old age and alcohol: Mr. DeAngelo insisted he had once had terminal stomach cancer with liver metastases and it had just . . . gone away.

Digging out the original pathology report, Rosenberg confirmed, the man had once been diagnosed with terminal cancer. In the course of the gall bladder operation, Rosenberg took the time to carefully probe the man’s liver for the metastases he was sure he would find. But there were none. “I rushed out of the operating room,” Rosenberg later wrote. “This didn’t seem possible. There had been only four documented cases—not four a year in the United States, but four, ever, in the world—of spontaneous and complete remission of stomach cancer.” Mr. DeAngelo, he realized, “presented a mystery of ultimately enormous dimensions” [2]. Dr. Rosenberg went on to devote a substantial portion of his career to seeking ways to augment the body’s immune response. While at the NCI, he famously devised an experimental treatment for advanced cancer using cells engineered to produce tumor necrosis factor [3].

A colleague of mine once attended a medical seminar that veered into a discussion of the odd case of Mr. DeAngelo, an alcoholic who polished off several quarts of bourbon a week. A doctor had interjected: “Did the guy quit drinking after they told him he had cancer?” Told no, he had asked, amid his colleagues’ swelling laughter, “Well, then, what *kind* of whiskey did he drink?”

His question wasn’t entirely facetious. What had happened? Dr. Rosenberg’s bare-bones case report provides no clues: “No evidence of tumor or other masses could be found in the abdomen. No adenopathy could be palpated” [2]. To sift through the medical annals of such cases is to be confronted by accounts dry to the point of dessication. We are told next to nothing about who these people actually were, what occurred in their journey, or what they think was essential to their cure.

## REMARKABLE RECOVERY

Could the human side of these unusual cases yield hints about what causes such radical departures from normal disease progression? It was in pursuit

of this question that my coauthor, researcher Caryle Hirshberg, PhD, and I wrote *Remarkable Recovery*. The book grew out of our probing of some 60 medically verified cases of unexpectedly long survival or complete cure of advanced disease, mostly cancer. We chose the term “remarkable recovery” to counter the more common term “spontaneous remission,” a nomenclature implying such cases so elude scientific understanding they can only be relegated to a mystery zone.

We proposed a more embracing definition, including not just instances of outright disappearance of incurable pathology, but cases where healing mechanisms other than treatment might be surmised to have caused exceptional outcomes: living in equilibrium with disease for unexpectedly long periods of time, or radically delayed progression, or recovery following merely palliative procedures. We took care to verify each case. Our source materials were medical records, case reports, articles in referenced journals, patient and physician interviews, and psychosocial questionnaires.

Looking at these cases, it was clear many were the products of multifactorial processes that would not lend themselves to the fine parsing of Occam’s Razor. The phenomenon of remarkable recovery may be produced by a cascade of biologic response modifiers we do not fully understand, including alternative medicines, quirks in the genetic make-up of the host or the tumor, mind-body mechanisms, psychosocial factors, or—most challengingly—all of the above.

## PSYCHOSOCIAL INTERVENTIONS

There has been much controversy over whether psychosocial intervention can affect disease progression. Frequently cited in its favor is a 1989 study by Dr. David Spiegel, which found that women with metastatic breast disease who received group therapy were more likely to be alive 18 months after diagnosis than a control group. However, several subsequent studies have failed to bolster this finding. Typical was a 2007 study, in *Psychooncology* [4], of the impact of supportive-expressive group therapy (SEGT) on survival in 485 women with advanced breast cancer. The trial found that although SEGT did improve quality of life and afforded protection against depression, there was no prolonged survival (median was 24.0 months in SEGT, and 18.3 months in controls).

Another 2007 article in *Cancer* [5] by Dr. Spiegel, detailing his 14-year study of 125 women with metastatic breast cancer, created a stir when his results failed to replicate his prior study. Women placed in group therapy in the new study had survived an average of 30.7 months, compared with 33.3 months for the control group. “Group therapy not a boost to cancer survival after all,” summarized a headline in the *San Francisco Chronicle*. “Psychologic support doesn’t extend life for most breast patients” [6].

Behind the word “most,” however, lay a finding of potential significance. A small subset of women with estrogen-negative breast cancer showed markedly better survival times with group therapy: 30 months versus 9 months for those who did not get therapy. The reason, Spiegel speculates, is that medical treatments for estrogen-positive breast disease have improved to such a degree

(ie, hormonal treatments such as aromatase inhibitors) that psychotherapy provided little additional boost for survival. But in the case of estrogen-negative breast cancer, where treatment has not shown similar advances, the psychosocial intervention of group therapy seemingly made a difference.

It will take follow-up studies to determine if this result is borne out. But the animating question in Dr. Spiegel's work remains: How can physicians maximize the healing resources of their cancer patients? Do such resources even exist, or are the mechanisms of psychoneuroimmunology or biospsychosocial medicine too subtle—or chimerical—to substantially alter the course of disease? That is, do the patient's thoughts, emotions, and social relationships have genuine clinical significance beyond improving attitudes and making patients subjectively "feel better"? It is a question with profound implications for therapeutic design and for the patient's own journey.

### **BIOLOGIC MODIFIERS**

Still, do such hard-to-quantify factors even need to be invoked? Various physiologic mechanisms and endogenous biologic response modifiers have been flagged as potentially relevant to cancer regression [7], including increased blood flow to (or elevated temperature at) the tumor site, actions by neuropeptides, changes in the body's biochemical "terrain," mobilization of immune factors, and genomic anomalies in host or tumor.

Everson and Cole [8] reported cases where people recovered after a mere biopsy, indicating a possible rousing of the immune system to combat tumors. Some recovered following transfusions of plasma and blood, hinting at the existence of blood-borne components that might react against the deadly interloper. Others had regressions after infections and high fevers. In the late nineteenth century, Dr. William Coley discovered a terminal sarcoma patient who had fully recovered following a severe streptococcal infection of the skin. Through trial and error, Coley devised a combination of streptococcal bacteria that reliably produced fevers of 104 degrees or more when injected at tumor sites, leading to unusual rates of remission. Coley [9] eventually documented a nearly 50% 5-year or more survival rate in 210 cases of soft-tissue sarcomas after induced infections and fever. However, as one researcher told us, "With Coley, tumor necrosis factor was only one short-lived piece of a cascade of effects orchestrated within the system. I'm not sure you can ever isolate some single active ingredient in the lab" [10].

### **DIET**

This problem of isolation applies even more to changes in diet frequently reported by remarkable recoveries. These run the gamut from eating large quantities of meat to switching to entirely vegetarian diets (one woman who had an unexpected healing of malignant melanoma ate "nothing but grapes" [11]). Harold Foster [12], who reviewed 200 cases of remarkable recovery, found that nearly 88% reported making substantial dietary changes, "usually of a strict vegetarian nature," before their healing. But were these causative

or concomitant? Retrospective studies of nutritional methods (eg, the so-called Gerson method [13] that features coffee enemas and copious quantities of carrot juice) have yielded intriguing findings but no acceptable level of proof.

### MIND-BODY MODALITIES

What of possible mind-body modalities? In a January 2008 *New York Times* article, the cancer specialist Dr. Jerome Groopman wrote: “[D]espite several decades of concerted research in the field of psychoneuroimmunology, to my scrutiny no robust effects of meditation or other relaxation techniques that could combat illnesses like cancer or AIDS have been identified” [14].

Is this a fair statement, or are there mechanisms whereby such practices might play a role in the healing process? The pathways of psychoneuroimmunology, for example, may be startlingly precise. The *International Journal of Neuroscience* published an almost eerie experiment in “voluntary modulation of neutrophil adhesiveness” [15]. Students were taught self-hypnosis and visualization techniques, then given a description of the neutrophil’s special functions and properties, focusing on the immune cell’s ability to adhere. Subjects were told to devise their own personalized visual imagery to attempt to increase this property of stickiness. (One student, for example, imagined her neutrophils as Ping-Pong balls with honey oozing out, causing them to stick to whatever they touched.)

After two weeks of such training, saliva and blood samples were compared with those obtained before the experiment had begun. The samples were analyzed for neutrophils and other immune components: monocytes, lymphocytes, and platelets. There was no difference in any of the cell counts before and after. The only statistically significant change was that the neutrophils’ ability to stick to foreign objects had increased.

A 1997 study of the effect of relaxation and guided imagery on the parameters of host defenses in women with advanced breast disease revealed increases in lymphokine activated killer (LAK) cell activity, and increased the total number of T cells (CD2+), mature T cells (CD3+), and activated T cells (CD25+). The intervention also reduced the circulating levels of tumor necrosis factor-alpha, though the clinical significance of these changes in terms in tumor biology could not be determined. Investigators also observed that the more vivid the imagery, the higher the natural killer (NK) and LAK cells’ activity [16]. In a later prospective randomized, controlled trial by the same investigators—this one with a group of 96 women with newly diagnosed large or locally advanced breast cancer—imagery ratings were positively correlated with clinical responses.

But the investigators also noted, “The problem with univariate analyses is that the different variables are often themselves intercorrelated: what we really want to find out is which variables are genuinely *independent* predictors of survival” [17].

### MULTIFACTORIAL HEALING

One case I studied, a man named Peter Hettel [11], speaks volumes about the difficulty of ferreting out such “independent predictors,” even as it suggests

unconventional factors contribute to outcome. Hettel had been diagnosed at MD Anderson Cancer Center with an immunoblastic sarcoma in his sinus. The mass was debulked with laser surgery, but quickly began to grow back. The recommended treatment—removal of the sinus and pituitary gland, radiation, and possible blindness as a side effect—was refused by the patient.

Among other things, Hettel had devised a vivid set of visualizations: “I’d imagine white immune cell bunny rabbits feasting on fields of orange cancer carrots, which increased [the rabbits’] energy and sex drive, which made them make more bunnies who were also hungry to eat more cancer.” One morning months later, Hettel recalls, “I couldn’t find enough carrots for all my rabbits. I thought, ‘Gee, I hope my bunnies are all right’” Not long after that, he had a vivid dream in which he was standing in a “cave of flesh” that had “big, pink, bulbous stalactites hanging down. . . . [T]here was an earthquake, and . . . they crashed down from the roof to the floor.”

A week later, while doing a yoga exercise, Hettel had an eruptive nosebleed. Running to the sink, he says, “I began to spit up what seemed like pieces of pink rubber eraser.” Probing the roof of his mouth with his tongue, he was shocked to find a hole instead of the tumor’s familiar protrusions. The doctor who had followed the case confirmed Hettel’s story: “It was as if his body had rejected a foreign object, like a transplant rejection . . . I can’t account for it, other than he seemed to change his living habits dramatically, adopted a take-charge attitude instead of just giving up. He began doing what he deeply wanted to do.”

Hettel tried a variety of other markedly nontraditional modalities, as is often the case with remarkable recovery, where patients tend to mobilize every possible healing resource at their disposal, not worrying much about whether one or the other was the most “active ingredient.” In addition to his visualizations, Hettel adopted a stringent health food diet laced with liberal quantities of carrot juice, and took up yoga and Zen meditation. He met a therapist who taught him alleged techniques for “neurologic repatterning.” Her therapy also encouraged “self-love,” producing episodes in which, Hettel reported, long-ignored emotions poured out and left him “mewling like a baby.” A week before his tumor was expelled, he had a highly emotional argument with his father and “for the first time in my life . . . I just openly and honestly expressed my anger toward him.”

## **IMMUNE RESPONSE AND EMOTIONS**

Is what a psychiatrist would call “emotional catharsis” relevant to the healing process? Candace Pert, codiscoverer of endorphins, suggests: “Since immune cells have neuropeptide receptors, the biochemistry of emotion is mediating the migration of natural killer cells through the body.” Because tumor cells also have such receptors, emotions, she suggests, may mediate their movements as well. Studies of potential negative biologic response modifiers—the immunosuppressant effects of stress, for example—also imply that emotions could be relevant to cancer progression. Other investigators urge considering

not only how stress affects the immune surveillance that helps govern tumor survival, but how stress contributes to “somatic mutation and genomic instability . . . It is possible that a sharper focus on other relevant biological processes such as increases in DNA damage, alterations in DNA repair, and inhibition of apoptosis, may explain more of the variance in disease outcomes” [18].

Is it possible, then, that states of relaxation or joy or emotional release would disinhibit apoptosis and promote DNA repair? It is provocative to wonder if one implication of psychoneuroimmunology is that many things are “medicine”: could encouraging words from a physician, a loving relationship, a strong emotion, a vivid image all produce physiologic cascades that can influence disease outcomes?

A valid critique is sometimes lodged that such formulations may contribute to a “blame the victim” paradigm. “If I’m not getting well,” a patient might reason, “I must not be trying hard enough.” Patients may blame themselves for not cultivating the “right” attitudes or behaviors to affect the blind machinations of biology.

At the same time, properly framed, patients may be encouraged to develop coping strategies more conducive to general health and happiness, though these necessarily will vary from person to person. Investigator Lydia Temoshok [19] has suggested, for example, that the most positive factors in health maintenance are what she dubs the “Three Cs”: control, commitment, and challenge. But for another person, it might be cantankerousness, compassion, and congruence. Still, of all the candidates for a “fourth C,” I would firmly nominate “connection.”

## **SOCIAL CONNECTION**

Time after time, strong social connection has been prominent in cases of remarkable recovery: enduring marriages, devoted friendship, indestructible love. Many of these patients were able to mobilize social networks. Some reported that just one person’s encouragement—whether a friend, a therapist, a doctor or nurse, or social worker—sustained them in their struggle against horrendous odds and formed the pivot point of healing.

The great majority of remarkable recoveries we studied had been married over 20 years, and 41% had been married over 30 years [11]. Studies have found that married persons live longer, “with lower mortality for almost every major cause of death, in comparison with single, separated, widowed, or divorced persons.” Conversely, in one study of more than 27,000 cancer cases, it was found that unmarried persons had markedly poorer rates of survival [20].

In one study of leukemia patients preparing to undergo bone marrow transplants, 54% of those who said they had strong emotional support from their spouses, family, or friends were still alive after 2 years, while only 20% of those who said they had little social support had survived [21]. Concludes one recent study: “The link between personal relationships and immune function . . . is one of the most robust findings in psychoneuroimmunology” [22].

The effect of social relationships may be traceable down to the cellular level. A recent (2005) study in the *Journal of Clinical Oncology* on the impact of social support and similar factors in ovarian cancer patients examined the relationship among distress, social support, and NK cell activity, peripheral-blood mononuclear cells, ascitic fluid, and tumor-infiltrating lymphocytes. The conclusion: “Psychosocial factors, such as social support and distress, are associated with changes in the cellular immune response, not only in peripheral blood, but also at the tumor level” [23]. The implications are profound: strengthening loving, supportive ties with others may be a vital therapeutic modality.

## ISSUES IN RESEARCH AND APPLICATION

How can a factor like love or community be applied in a treatment regimen? How can any of these foregoing observations be applied? Whether or not a more extensive study of remarkable recovery produces legitimate (ie, replicable) therapeutic strategies with consistent and measurable results, increased study would surely yield suggestions for therapeutic design that augments not only the patient’s will to live, but his or her joy in living.

Mind-body therapies are often portrayed in the literature as self-palliative, adjunctive, and complementary, but rarely as contributive to cure. Many physicians continue to view them as acceptable indulgences so long as they are harmless and the patient remains fully compliant with a standard treatment regimen. The possibility that such modalities might help drive the healing process itself is infrequently acknowledged. Observations of remarkable recovery may mandate we broaden the definition of “medicine” to include biopsychosocial factors that positively impact what Norman Cousins [24] once dubbed the “healing system” (which he defined as “a grand orchestration . . . enabling human beings to meet a serious challenge”).

It seems especially important to encourage physicians to publish their cases of remarkable recovery in referenced medical journals so that a true epidemiology of this phenomenon can emerge. The study of the odd, the unexpected, the hard-to-find and difficult-to-quantify has always been the challenge and glory of medicine. (The study of autoimmune disorders, for example, crucially advanced our knowledge of immunology.) But there has been scant methodologic study of remarkable recovery, not in small part because of how infrequently these cases are reported in the literature. This is not necessarily a reflection of their rarity, but a reluctance to write up these anomalies [25].

As suggested earlier, the scarcity of reports also stems from the lack of an appropriately broad definition that includes unexpectedly long survival, recoveries that were treated conventionally yet “shouldn’t have happened,” unusual recoveries resulting from a combination of conventional and alternative treatment.

## A REMARKABLE RECOVERY REGISTRY?

Most reports contain precious little information about the individuals who are their subjects. Attempting to locate the actual patients behind the often-sketchy



descriptions, I was surprised to discover how many doctors had lost track of their exceptional patients entirely. How can the scattered data on the subject be retrieved from its orphaned status in medicine? A Remarkable Recovery Registry modeled on (or perhaps even included within) the National Cancer Institute's Tumor registry might be a cornerstone.

New methods of interviewing and reporting are also needed. Each patient's unique characteristics may be as vital as his or her physiologic measures. Some of this information might be best obtained from a support person, whether family member, nurse practitioner, or social worker, likely to be familiar with the dimensions and details of the person's life. The patient's account of his or her experience, often dismissed as merely subjective, could also be considered as a source of data, particularly in the context of "the healing system."

By re-examining current therapeutic strategies in the context of possible mind-body factors brought to light in remarkable recovery, the testing of new medical protocols could be enhanced to the benefit of patients as well as medical treatment and education. The picture of the spectrum of self-repair could be broadened. Adding psychosocial assessments to intake procedures could lead to individualized treatment models. Gathering and analyzing solid data on remarkable recovery would give the concerned physician a means to provide "ethical hope" to even terminal patients. If remarkable recovery contains a social dimension, then placing focused attention on social support would become an essential component of medical treatment.

Are there genetic or other biologic anomalies in remarkable recovery patients? In *Remarkable Recovery*, we cite the case of a Seattle man who experienced a spontaneous regression of bronchogenic carcinoma [11]. The man's inquisitive physician, Dr. Bell, who wrote up the case twice for the *American Journal of Surgery*, incubated some of the man's lymphocytes and placed them in a Petri dish with another patient's lung cancer cells. While putting one patient's white cells in proximity to another's cancer cells would normally have little effect, Dr. Bell noted with surprise that his patient's leucocytes reduced the cancer cells' colony formation by more than half [26].

A Remarkable Recoveries registry would have a tumor bank and a plasma bank. A rigorous analysis of tissue and cells of enough individual cases could lead to a wealth of biologic information. With the advent of genomic testing and tools for cloning rare biologic factors, medical science is in a unique position to make groundbreaking discoveries about unique tumor-host mechanisms based on remarkable recovery cases.

Along with any insights into mechanisms of cure, cases of remarkable recovery have much to teach us about optimum ways to address the full spectrum of cancer patient needs. Should not all medical students learn skills that could help their patients mobilize the psychological, emotional, and spiritual resources that may be a form of medicine? One survey showed that 90% of 649 oncologist respondents believed that attitudes of hope and optimism, a strong will to live, confidence in the doctor, and emotional support from family and friends had been of significant benefit to treatment [26].

## A SOURCE OF HOPE

I was recently contacted by a woman, Karen Dennis (Karen Dennis, unpublished manuscript, 2008, quoted with permission), who had a well-documented remarkable recovery (from metastatic carcinoid cancer of the ampulla of Vater). Her case may exemplify a model of doctor and patient working together to maximize all the healing resources at their mutual disposal. Dennis's journey ran the gamut from conventional treatment, to homeopathy, to cutting edge experimental chemotherapy, to a radical surgery opposed by five of six surgeons on her hospital tumor board. When, despite heroic medical efforts during an 11-year period, her metastases returned, she had decided to refuse further treatment and pursue a range of alternatives.

Dennis reports that "she struck a bargain" with her primary care physician, asking for his support in abandoning oncology and promising that if or when she became symptomatic again, she would submit to whatever diagnostic work he felt appropriate. He assented and, she reports, wrote her an unusual prescription:

You have my permission to NOT accept your diagnosis.  
You have my permission to NOT accept your prognosis.  
Permission to be selfish and celebrate the miracles in your life.

This, Dennis says, "turned out to be the most compliant I had ever been with a treatment plan." When, 4 years later, she had her first CT scan since making her "compliant" decision, there was no evidence of disease. Her surgeon, Dr. John E. Niederhuber, who had in the interim become director of the National Cancer Institute, wrote her a letter that could serve as a template for how physicians might relate to such remarkable cases.

"I do not have a ready explanation for the miraculous recovery you have experienced," he wrote. "Because of cancer's complex nature, and the uniqueness of each individual affected by the disease, unexpected cures can rarely be attributed to any one factor: the nature of the care received, the treatment(s) delivered, specific disease or patient characteristics, or environmental or social influences. From a personal perspective, however, I have come to understand that the capacity to heal is based in part on a successful patient-doctor partnership" [27].

Dennis calls "the sweet success" of her collaboration with Dr. Neiderhuber and her primary care physician "the tipping point toward healing versus the inevitable march toward my prognosis." Yet, she sounded a wistful note in a letter to me: "It has bothered me a great deal," she wrote, "that when this patient has documented evidence to support physiologic change that falls outside the margins of accepted allopathic paradigms, no one seems to have any questions. Perhaps I am naïve . . . but you would think medicine would be intensely interested in people who have done what they said couldn't be done" [28]. I could only reply to her that I felt certain the day was not far off.

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