The History of the Enzyme Treatment of Cancer

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Although there exists some debate over who discovered pancreatic enzymes, it appears the French physician Lucien Corvisart first described trypsin in 1856. However, the German researcher Julius Kühne deserves credit for actually naming this protease in 1876 and for introducing the concept of digestive enzymes as catalysts secreted by the pancreas that allow for efficient breakdown of food in the gastrointestinal (GI) tract.

By 1900, the 3 main classes of pancreatic enzymes had been identified: (1) the proteases that cleave proteins into constituent amino acids and peptides; (2) the amylases that reduce complex carbohydrates into simple disaccharides and trisaccharides; and (3) the lipases, which convert triglycerides into monoglycerides, diglycerides, and free fatty acids. Physiologists at the time, aware these enzymes worked best in a slightly alkaline environment, discovered that the pancreas released these various ferments, as they were called, into the duodenum during meals along with bicarbonate to neutralize the acidic chyme arriving from the stomach.

By the late 1800s, there was a flurry of activity among European researchers searching for therapeutic applications for the newly discovered enzymes, above and beyond any purely digestive use. Scientists discovered that trypsin could be useful in the treatment of diphtheria when applied directly to the tough fibrous membrane formed in the throat that could, if unchecked, lead to suffocation. In an animal model of the disease, a preparation of trypsin applied in the larynx appeared to digest away this tissue and when tested in humans, the enzyme worked quite well. An early reference to the successful treatment in humans dates from the October 23, 1886 issue of the *Journal of the American Medical Association.*[1]

In response to these early successes, by 1900, 2 pharmaceutical firms, Merck and the New York–based Fairchild, affiliated with Burroughs Wellcome, marketed powdered trypsin preparations derived from animal sources for treatment of the disease as well as injectable preparations for a hoped-for systemic effect. In addition, preparations meant for oral ingestion as a digestive aid became available, the most widely prescribed known as Holadin.

In 1902, the English scientist John Beard, DSc (1858-1924), Professor at the University of Edinburgh in Scotland, first proposed an anticancer activity for trypsin. His thesis, which would generate considerable controversy at the time, represented the culmination of some 20 years of meticulous research that began with the development of the nervous system in invertebrates.

Beard was not a physician but a zoologist trained as an embryologist: His graduate studies at the University of Freiburg in Germany, from which he received his doctoral degree in 1884, dealt with the embryogenesis of the sense organs in an obscure worm.[2] As his career evolved, he focused his attention on the developing nervous system of fish, then eventually mammals, and many of his pioneering findings from this period in his life, now proven correct, are standard fare in contemporary embryology texts.

It was Beard's study of the embryonic nervous system that, through a most convoluted route, led him to consider the formation and growth of the placenta, which anchors the mammalian fetus to the uterus and serves as the point of connection between the maternal blood vessels, providing oxygen and essential nutrients, and the blood of the embryo carrying the wastes of metabolism.

Beard was the first scientist to report that in many respects the placenta in its early stages—known as the trophoblast (from the Greek "to feed or nurture")—looks and

behaves much like a cancer. Though we might think of the late 19th and early 20th centuries as a primitive time in medical research, by 1900 institutions devoted to cancer research, such as Sloan-Kettering in New York, were already up and running, with large staffs of scientists working to unravel the biology of cancer. By Beard's day, investigators had adeptly described the histology, behavior, and even the chromosome aberrations seen in the many varieties of malignant disease.

Cancer cells, it was well known at the time and as we agree today, possess certain well-defined characteristics. In appearance under a microscope, they display a primitive undifferentiated phenotype; in terms of behavior, they proliferate without restraint, can invade through tissue boundaries such as epithelial linings, and can migrate through organs while producing an extensive blood supply needed to support the characteristic exponential growth of malignancy.

Beard pointed out that the trophoblast begins as a very cancer-like tissue. It forms as an undifferentiated offshoot from the earliest stage of the embryo in the blastocyst phase, and its cells initially proliferate exponentially. The cells easily invade and migrate through the uterine epithelial lining and underlying stroma (an ability not seen in any other tissue except cancer) while, like a tumor, generating a rich blood vessel connection to the uterine maternal arteries and veins needed to maintain embryonic life. In terms of the last point, though the word *angiogenesis* is a modern term, Beard and his colleagues understood the concept quite well: the need for both tumors and the trophoblast to stimulate new vessel formation to allow for survival.

Beard was not only the first to note the similarities between the trophoblast and cancer, he went a huge step further in his thinking, claiming that cancer, whatever the histologic type, is fundamentally trophoblastic in its actual cellular origins. In laboratory experiments with animals, Beard found that during embryogenesis, many of the cells of the early trophoblast do not end up within the placenta itself but migrate throughout the various developing tissues and organs of the fetus to form undifferentiated nests that remain in place for the duration of the organism's life. Should these misplaced trophoblast cells be stimulated into reproductive activity through inflammation or infection, in the wrong place and at the wrong time, they become the invasive, exponentially growing tissue we identify as cancer.

Not surprisingly, Beard's scientific colleagues of 110 years ago could make no sense out of what he was saying, because no one else could identify these misplaced, "vagrant trophoblasts," as Beard called them, nor understand how they could form a cancer. Scientists believed then, as they were to believe for most of the 20th century, that cancer develops from mature differentiated cells in a tissue or organ that through some elaborate metamorphosis revert to a primitive morphology. In the process, these cells develop the hallmarks of cancer not seen in normal healthy tissues: an undifferentiated phenotype, unlimited proliferative potential, the ability to invade through tissue boundaries such as the basement membranes of epithelial linings, the ability to migrate through dense underlying stroma, the ability to metastasize, and the necessary ability to rapidly produce an ever-growing blood supply.

From a contemporary perspective, Beard, though discounted in his lifetime, may have been correct on all points. Scientists such as Murray and Lessey[3] at the University of North Carolina, and Ferretti[4] in Europe, have rediscovered the placental trophoblast as the ideal model for the study of cancer morphology, behavior, and molecular biology. As it turns out, cancer uses the same molecular mechanisms, the same transcription factors to turn genes on and off, and the same matrix metalloproteinases to invade through tissue boundaries and stroma as does the trophoblast. Further, those nests of primitive cells located in our various tissues Beard claimed to have identified were most likely what we today call stem cells. The concept of stem cells wouldn't enter our modern scientific consciousness until some 40 plus years after Beard's death, when in the 1960s McCulloch and Till,[5] evidently unaware of Beard's earlier work, would claim the discovery of these nests of undifferentiated cells that we now know are necessary for life. They provide an essential reservoir to replace cells lost due to normal turnover along the intestinal tract—which sloughs off every 5 days—or those lost due to injury, disease, or apoptosis.

As further confirmation of Beard's hypothesis, beginning in 2002 with Dr Wicha's work at the University of Michigan,[6-9] scientists at multiple institutions have been demonstrating that cancer does not develop as so long thought from mature, differentiated healthy cells that suddenly go molecularly berserk, transforming into the undifferentiated, invasive tissue of cancer. Instead, these investigators are showing rather convincingly that cancer develops from stem cells that lose their normal regulatory restraint.

Be that as it may, Beard well knew that in its normal timeline of growth, the trophoblast differed in 1 key regard from a cancerous tumor. At a specific point after conception—Beard claimed day 56 in humans—the trophoblast normally abruptly changes from a poorly differentiated, rapidly proliferating, invading, angiogenic tissue into the mature, highly differentiated, nonproliferating, noninvasive placenta. In its final incarnation, the placenta, a circular plate-like organ imbedded within the uterus some 8 to 10 inches in diameter and 1 to 2 inches thick, consists of a variety of well-differentiated cell types with minimal reproductive and no invasive potential. Thin-walled septa divide the placenta into sections like slices of a pie, with the mother's blood percolating on one side and the embryo's on the other.

In Beard's mind, the transformation of the early cancer-like trophoblast into the mature placenta was quite a remarkable biological feat, a process that became an obsession for him. Because he believed that cancer was not only *like* the trophoblast in its microscopic appearance and behavior, but was trophoblastic in its origins, he assumed if he could determine the factor or factors responsible for the change in trophoblastic character as the placenta formed, he would have the solution to cancer.

After years of research, Beard came to the conclusion that the key was in the embryonic pancreas. As witnessed in every mammalian species he studied, the very day the trophoblastic placenta converted from a poorly differentiated, invading tissue into the mature placenta, the embryonic pancreas began synthesizing and secreting its coterie of digestive enzymes. Contemporary molecular biologists have confirmed that the fetal pancreas does become active approximately when the trophoblast begins transforming into the mature placenta.[10,11]

Because it seemed pancreatic enzymes regulated trophoblast development, Beard logically assumed these same "ferments," in addition to their well-characterized digestive function, must be our main defense against cancer, keeping the "vagrant trophoblasts" in control, and would in turn also be useful as a cancer *treatment.*

After announcing his "trophoblastic theory of cancer" in a *Lancet* article in 1902,[12] Beard would first test his thesis in an animal tumor model available at the time, the Jensen's mouse tumor, what appears to have been a sarcoma-like malignancy. With 6 untreated tumor-laden mice as controls, after Dr Beard injected an extract of trypsin into 2 mice growing such cancers, the tumors completely regressed.[13] Subsequently, during the mid and later part of the first decade of the 20th century, a number of physicians interested in Beard's hypothesis began, under his direction, to use injectable pancreatic enzymes to treat their human cancer patients. The first report I have been able to locate, appearing in the *Medical Record* in November 1906 and written by New York physician Clarence Rice, was entitled "Treatment of Cancer of the Larynx by Subcutaenous Injection of Pancreatic Extract (Trypsin)" with the subtitle "A Case of Growth, Supposed to Be Carcinoma, Cured."[14] The history and results in this case with enzyme treatment were, in the author's estimation, "a remarkable cure." As an aside, Dr Rice recommended the Fairchild injectable preparation along with the oral supplement "Holadin."[14]

A month later, in December 1906, another New York physician, Margaret Cleaves, described 2 patients in the *Medical Record,* the first a woman with a recurrent large tumor of the tongue that stabilized on the enzyme treatment.[15] At the time of the publication, the patient hadn't been on the therapy very long but seemed to be improving substantially. The second case, a man with a large inoperable rectal carcinoma, experienced tumor necrosis, tumor liquefaction, and finally its sloughing off with the trypsin injections. Other case reports of successfully treated patients appeared in the major medical journals of the day, including the *Journal of the American Medical Association*[16] and the *British Medical Journal,*[17] describing apparent cures of patients diagnosed with head and neck, inoperable uterine, colorectal, and metastatic breast cancers.

During his lifetime, Dr Beard recommended only injectable preparations of pancreatic enzymes as a cancer treatment, assuming that for his specific purposes, orally ingested preparations would be of little value. It was generally believed then—as is still believed today—that trypsin, like any other protein ingested by mouth, would be degraded by the hydrochloric acid present in the stomach. Any active trypsin molecules that might survive this initial assault would then be subjected to autodigestion within the alkaline duodenum. Even if some trypsin did remain beyond this point, scientists already knew the protease to be a fairly large molecule that, they believed, could not possibly pass through the intestinal mucosa for systemic effect. In his classic textbook of the day, *Collected Contributions on Digestion and Diet,* the eminent physiologist Sir William Roberts, MD, made the case that orally ingested pancreatic enzymes would not survive very long in the digestive tract.[18]

By 1907, the initial successes reported in the literature generated considerable interest in Beard's enzyme treatment of cancer. In response to this enthusiasm, a growing number of firms began selling their own "trypsin" specifically as a cancer treatment in addition to those available from Merck and Fairchild. With trypsin formulations widely available, physicians both in the United States and in Europe began applying the therapy, usually without consulting Beard, and with variable results. As both positive and negative reports began to filter into the literature, Beard began to suspect that many of the available preparations had little potency and, hence, little efficacy.[19]

From our readings in the literature, it seems that in Beard's era, the manufacturers used a very simple process to extract the enzymes, first mincing the glands in cold water, pressing the mixture, then removing the active component with an alcohol solvent. The alcohol would then be allowed to evaporate off, leaving the desired enzyme fraction.[20] However, pancreatic enzymes are quite unstable over time in an aqueous environment, prone to autodigestion. We suspect the procedure used in Beard's day was neither exacting nor refined, the final preparation, most likely, containing little in the way of potential enzyme activity. To make matters worse, those products intended for injectable use were provided in solution in vial form, an ideal environment for the autodigestion process to begin. Fairchild did market a dry powdered "trypsin" meant to be mixed with water immediately before injection, but even this proved so unstable that by 1907, as Beard reported, the company discontinued its sale.[12]

In the November 16, 1907 issue of the *Lancet,* P. Tetens Hald, MD, "Formerly Assistant in the Pharmacological Institute of the University of Copenhagen" and a Beard proponent, published the results of his evaluation of 6 popular enzyme products available at the time, including those marketed by Merck and Fairchild.[21] In his research, he employed the same method used today to assess proteolytic activity, the casein digestion test. This simple assay measures the amount of the milk protein casein curdled over time by a known quantity of pancreas product.

Dr Hald contacted the manufacturers of the various products he analyzed in his laboratory, none of whom provided him with any information about the stability of the formulations

they sold commercially. To his surprise, his assays revealed the potencies varied enormously, up to a factor of 400, and that the activity levels rarely correlated with the company's claims, as stated on the bottle or in its literature.[21]

In his 1911 book *The Enzyme Treatment of Cancer*, Dr Beard himself bemoaned the dearth of standardized and potent enzyme preparations, a situation that led to inevitable treatment failures when physicians used products of poor quality. He actually quoted a Merck publication from the time, in which the writer discussed the confusion in the field:

> The actual position of affairs in the past few years can best be described by quoting the impartial opinion of a competent author. On p. 340 of *E. Merck's Annual Report of Recent Advances in Pharmaceutical Chemistry and Therapeutics* (Darmstadt, vol. xxii., August, 1909) one may read regarding trypsin: "The mode of action and the value of pancreas preparations in cancer has not yet received a wholly reliable explanation. Great difficulties are encountered because the preparations used by the various investigators differ greatly in respect to their chemical properties, their purity, and in the amount of active substances they contain, and often these factors are not fully known to the student of the literature, or to the physician who has used them and describes their action. Further difficulties arise when pancreatin [whole pancreas product] and trypsin are described as substances of equal value, and how shall we gauge the action of pancreatin and trypsin ampullae whose mode of preparation and whose composition is not mentioned in the original paper, neither is there any mention made of their sterility or the method by which they have been sterilized? … So long as the solutions of pancreatin and trypsin are treated as secret remedies no one will be able to form a clear picture of the value of trypsin treatment from the many publications which have appeared."[12]

In reference to the above, as an aside we find it interesting that by 1909, Beard's hypothesis had generated interest sufficient enough to warrant thoughtful discussion in the annual report of a major international pharmaceutical company. This exposition also supports Beard's contention that the mixed results for enzyme treatment being reported in the literature most likely reflected no flaw in the theory, only variations in the quality of product.

Despite the initial enthusiasm for Beard's trophoblastic hypothesis and the clinical enzyme treatment, ultimately the medical community at large seemed to have mobilized an angry backlash against Beard and his followers. He was attacked in medical journals and newspapers, and he was belittled at scientific conventions. Nonetheless, Dr Beard stuck to his course and fought back in articles and letters to the editor, and in *The Enzyme Treatment of Cancer,* a text that outlined his years of research and the promising laboratory and clinical results.[12] Regardless, interest in Beard's thesis gradually petered out, and when he died in 1924, he died frustrated, angry, and ignored, his therapy already considered no more than an historical oddity.

Though the rejection of something new in the scientific research community hardly seems surprising—it is of course the historical norm—I find the ultimate indifference toward, and contempt for, Dr Beard evident in his contemporary academic colleagues most unfortunate. Beard was, after all, an impeccably trained scientist, a professor at an eminent European university whose embryological findings are still accepted in the texts of our day. He carefully documented his laboratory and clinical results that he published in the conventional medical literature. But it seems to have made no difference at all.

A number of factors contributed to the decline of interest after 1911 in Dr Beard's trophoblastic hypothesis and his enzyme approach to cancer. Certainly, the enthusiasm for the X-ray, discovered in 1895 by Röntgen, helped push Beard's treatment into the background.[22] After all, at the same time Beard was arguing his case, 2-time Nobel Laureate Marie Curie, widely admired and respected at all levels of society, had vigorously championed the mysterious invisible rays as a nontoxic cure for all cancer, a breakthrough the press promoted with great enthusiasm. Beard, on the other hand, had no such media savvy science star to praise his ideas about the use of enzymes against malignant disease. And it would not be until after Beard's death in 1924 that researchers began to appreciate the severe limitations of radiation treatment, which in reality worked well against only a few cancers. Even for those tumors that did respond initially, usually the disease recurred with a vengeance and the therapy once thought to be harmless, actually as all physicians know today, could be quite toxic. An entire generation of radiation researchers died as a result of cavalier exposure to the rays, including Marie Curie herself who eventually succumbed to radiation-induced aplastic anemia.[24] By then, Beard was long forgotten.

Above and beyond the realities of scientific politics, we suspect that poor quality enzyme products did much to undermine Beard's treatment. In a sense, Beard was a victim of his own fame. The initial successes reported in the literature prompted many doctors to begin using any number of enzyme formulations without first consulting Beard about dosing and quality, with inevitable poor or mixed results. The disappointments fueled the criticism in the journals, to the point that after 1911, few doctors of Beard's generation even considered the treatment for their patients.[25]

Though interest in Beard's cancer treatment dwindled, certainly after his death, injectable formulations of pancreatic enzymes remained available in the United States and Europe for treatment of diphtheria, along with oral preparations intended for treatment of digestive problems and pancreatic insuffiency.

By the 1940s, the commercial demand for pancreatic enzymes such as trypsin had expanded greatly beyond their limited pharmaceutical applications. For example, leather tanners used proteolytic enzymes to speed up curing, and candy manufacturers learned that trypsin, when added during the processing of chocolate, helped create a smoother product.

But the commercial suppliers still relied on the old mincing and alcohol method of extracting proteolytic enzymes from the animal gland, a very inefficient technique that gave a 10% to 15% yield.[20] A potential bonanza awaited anyone who might develop a more efficient enzyme purification process.

The biochemist Ezra Levin of Champaign, Illinois, active during the 1940s and 1950s and at the time one of the leading experts in the manufacture of pancreatic enzymes, believed he had done just that. His lengthy 1950 US patent entitled "Production of Dried, Defatted Enzymatic Material" detailed his crowning achievement, an elaborate multistep process for extracting active enzymes from the gland that he insisted was more efficient and more cost-effective than the previous methodology.[20] During his process, all fat, which he saw as waste, would be removed and importantly, most if not all the precursors such as trypsinogen would be activated, yielding a product of high potency with purported minimal processing losses—a product that Levin and his customers thought ideal for pharmaceutical as well as industrial use.

Levin had made 2 assumptions as he perfected his method. First, he believed that the fat in the gland—and the pancreas is a fatty gland—had no useful purpose beyond its role as a storage depot for excess calories and needed to be removed. To him, fat seemed little more than inert filler. Second, he always assumed the more activated the product, the better.[20]

Levin actually created a company, Viobin, for years a subsidiary of A. H. Robbins, to manufacture and market his enzyme products. The Levin method proved so successful that by the 1960s, Viobin provided most of the enzymes used in the United States, both for pharmaceutical and other industrial purposes. Even other manufacturers that ventured into the enzyme business themselves relied on variations of the Levin patent.

THE SALVATION OF AN IDEA

Though relegated to obscurity, during the 20th century, Beard's enzyme thesis did not disappear completely. Periodically, other physicians and scientists rediscovered his work, saw the potential benefit in his hypothesis, and kept the idea alive, however tenuously. During the 1920s and 1930s, a St Louis physician, Dr F. L. Morse, reported that he had successfully treated a number of advanced cancer patients with injectable pancreatic enzymes. When he presented his well-documented findings to the St Louis Medical Society in 1934—a proceeding published in the *Weekly Bulletin of the St. Louis Medical Society*—his colleagues attacked him viciously and relentlessly.[26] One physician at the session, a Dr M. G. Seelig, remarked, "While I heartily agree with Dr Allen when he strikes the note of encouragement, I recoil at the idea of witlessly spreading the hope of a cancer cure which is implicit in the remarks of Dr Morse this evening …"

Subsequently, Frank Shively, MD, a Dayton, Ohio surgeon active during the 1960s,[27] rediscovered Beard's earlier papers and used injectable formulations of pancreatic enzymes in his treatment protocols. In a self-published 1969 monograph, *Multiple Proteolytic Enzyme Therapy of Cancer*, Dr Shively reported on 192 cases of patients diagnosed with advanced cancer treated with injectable enzymes, with 12 apparent "cures." However, in 1966, the Food and Drug Administration, perhaps in response to Shively's growing reputation, forbade the sale of injectable pancreatic enzymes, and the surgeon seemed to have returned to more mundane medical pursuits.

Contemporaneously with Dr Shively, in the 1960s, William Donald Kelley, DDS, first appeared on the scene, with his complex cancer treatment involving a whole foods diet, large amounts of various nutritional supplements, detoxification routines such as coffee enemas, and prodigious doses of pancreatic enzymes ingested orally—but never injected.

Kelley claimed he discovered the anticancer properties of oral pancreatic enzymes without any previous knowledge of Dr Beard. Kelley had been a successful orthodontist with a serious interest in nutrition, practicing in Grapevine, Texas, when in the early 1960s, while he was only in his mid-30s, he became devastatingly ill. His doctors eventually diagnosed advanced pancreatic cancer, though he never underwent tissue sampling—not uncommon in the days before computerized tomography (CT) scans and core biopsies. In desperation, with 4 children dependent on him, Kelley through trial and error devised his own nutritional program to slow the disease, including an organic, largely vegetarian raw foods diet, a variety of supplements, and the coffee enemas. He also added high doses of oral pancreatic enzymes to his regimen, not because of any familiarity with Beard's hypothesis, but to help relieve his severe digestive distress—as occurs commonly in patients with pancreatic malignancy.

Kelley's digestion was so poor, he began ingesting huge amounts of pancreatin around the clock hoping to keep his worsening symptoms—including excruciating pain whenever he ate—at bay. He discovered that with large doses, his tolerance for food improved and, to his surprise, his large tumors, readily palpable through the abdominal wall, seemed to regress. Perplexed by his observations, he scoured the medical literature looking for evidence that someone else might have witnessed an anticancer effect for pancreatic enzymes. His search eventually led him to Dr Beard's book and papers from 50 years earlier, but by that point, as he claimed, Kelley had already worked out the rudiments of his treatment.

From that very personal experience began Kelley's foray out of conventional orthodontics into the controversial world of nutritional cancer therapeutics. By the late 1960s, having long abandoned dentistry, he refocused his attention on treating, with his nutritional regimen, the very ill drawn from all over the country, most diagnosed with advanced malignancy. With the publication of his 1969 book *One Answer to Cancer*,[28] Kelley for better or worse secured his position as a preeminent alternative cancer therapist and inevitably as a target for the mainstream medical world which then, as now, had little use for proposed nutritional approaches to the disease.

Kelley intently studied the writings of Beard, who strongly insisted the treatment needed to be applied via injection. Nonetheless, for the duration of his career, Kelley only recommended oral formulations. Though injectable preparations were still available in the United States during the early years of Kelley's nutritional practice, as a dentist, Kelley lacked the legal right to prescribe injectable enzymes. Even if such products had remained on the market and even if he had the authority to use them, his own experience treating himself, and his subsequent experience with hundreds of patients taught him that oral preparations worked very well.

I met Dr Kelley by chance during the summer following my second year of medical school in 1981. At that time, he seemed completely modest and unassuming, seeking only to have his work properly evaluated so that if the approach had merit, it might become more widely accessible to patients in need. I was fortunate to have as a mentor at Cornell Medical College the late Robert A. Good, MD, PhD, then president of the Sloan-Kettering Research Institute, who encouraged a review of Kelley's cases.

Under Dr Good's direction, I began a student project evaluating Dr Kelley's patients, methods, successes, and failures. During a rather extraordinary summer spent reading through Kelley's records in his main Dallas office, I quickly found evidence of what appeared to be patient after patient with appropriately diagnosed, biopsy proven advanced and even terminal cancer, who were alive 5, even 10 years since first beginning the enzyme therapy. What began as a mere student investigation eventually evolved into a full-fledged research project, completed while I was a fellow in Dr Good's group, which, after he left Sloan, moved first to the University of Oklahoma, then to All Children's Hospital in Florida.

As part of my project, I eventually interviewed and evaluated more than 1000 of Kelley's patients, concentrating on a group of some 455 patients diagnosed with cancer who had done well under his care. From this population, I wrote up in detail 50 cases, representing 26 different types of cancer. Even today, nearly 30 years later, I am still impressed by Kelley's achievement. For example, one of these patients, a woman who ran a gas station with her husband in Wisconsin, was diagnosed in August 1982 with metastatic adenocarcinoma of the pancreas, the worst form, with biopsy-proven metastases into the liver. The Mayo Clinic confirmed the diagnosis, offered no treatment, and told her she might live 12 months. With no conventional options recommended, she began looking into alternative approaches, learned of Kelley, and began his treatment.

I first interviewed her in 1986, 4 years after her diagnosis, as part of my Kelley investigation. At the time, still following her nutritional regimen, she reported feeling quite well. In the many years since, we have kept in touch regularly and today in 2014, she is alive, well, and as feisty as ever, now 32 years from her original diagnosis. She has never returned to her conventional physicians for follow-up radiographic studies, but to put her case in perspective, I have searched the literature repeatedly and know of no other similar patient with biopsy-proven liver metastases from pancreatic adenocarcinoma documented at a major institution, alive and well 32 years later.

Another patient was initially diagnosed with adenocarcinoma of the uterus in 1969. Because of the large size of the tumor, her doctors advised a course of intensive radiation therapy before hysterectomy. Because her doctors thought the disease was localized, postoperatively no adjuvant therapy was suggested.

However, by 1974, her general health had deteriorated significantly; she experienced unrelenting fatigue, severe depression, weight loss, and vague abdominal pains. Initially her physicians attributed her symptoms to "nerves," but when she developed a grapefruit-sized tumor in her pelvis, she was referred back to her surgeon. At that time, an X-ray revealed multiple tumors in both lungs consistent with metastatic disease. Her surgeon recommended palliative resection of the pelvic tumor nonetheless to prevent an impending intestinal obstruction, though he admitted to the patient she had an incurable disease. Subsequently, she underwent the suggested surgery then consulted with an oncologist who prescribed a synthetic progesterone, which he explained might prolong her life. But the patient experienced such serious side effects, she discontinued the drug after some 6 weeks and with no further options began investigating alternative treatments for cancer. After learning of Dr Kelley, she consulted with him and followed her prescribed nutritional program religiously.

Under Kelley's care, her health gradually improved. She avoided all conventional doctors for a time, but 9 years after starting her regimen, in 1984, she returned to her former primary care physician for evaluation of an irregular heart rhythm, a long-standing problem. The physician, as the records indicate, was astonished she was still alive. A chest X-ray confirmed total resolution of her previously described multiple pulmonary nodules. Subsequently, she kept in touch with me periodically until her death in 2009 at age 95, 34 years after her diagnosis of metastatic disease, some 40 years from her original diagnosis. To put her case in perspective, I have searched the literature and know of no similar patient with recurrent endometrial cancer who experienced total regression of disease and survival of 34 years after the appearance of extensive metastases.

During my investigation of Kelley's therapy and patients, as a side project I also tried to evaluate the relative efficacy of the different pancreatic formulations he had recommended during his time in practice. By the time I met Kelley in 1981, he had become convinced that the more active the oral product, the better the effect against cancer, insisting as well he wanted no precursors in his formulation. I even traveled with Kelley to Wisconsin in the summer of 1981 to meet with the manufacturer he used at the time to discuss with them his new plans for the strongest supplement possible, containing only fully activated, and defatted, pancreatin.

From Kelley's records and our conversations about the issue, I had a fairly good idea of which strength of enzyme he

used during which period, and from my review of his patient charts on a year-by-year basis, it seemed to me that his greatest success as a practitioner occurred during the period from 1970 to 1982, when he relied primarily on a modestly activated formulation containing a high percentage of inactive precursors. After he opted for increasingly more activated product, it seemed to me his success declined with the "stronger" preparation.

In any event, I finished my "Kelley Project" in 1986 and wrote up the results in monograph form hoping the unusual case reports would stimulate research interest in the therapy from academia. But despite Dr Good's support and 5 years of serious research efforts, I was unable to get the book published. Sadly, Kelley turned increasingly paranoid, at one point accusing me of being sent by the Central Intelligence Agency to steal his therapy for the government. He had shut down his practice and, after 1987, I had no further direct contact with Kelley. My monograph about Kelley's work was finally published in 2010 as *One Man Alone*, with a lengthy new introduction.[29]

When my colleague Dr Linda Isaacs and I arrived in New York in the fall of 1987 determined to salvage Kelley's treatment, we knew if we were to succeed in practice, we needed a reliable source of enzymes. As I thought about the situation, I realized we must determine the optimal composition for the enzyme product in terms of relative fat and protein content, as well as the ideal level of proteolytic activity—and hopefully find a source that met our specifications.

I had already begun to move away from the Levin methodology as the best for manufacturing pancreatic enzymes. I knew that he had designed his extraction method to remove as much fat as possible, which he perceived as useless filler. I thought in this regard, Levin, as well as Kelley who accepted without question Levin's dictates, had been wrong, and that fat might allow for a more stable product and provide physiological benefit. By 1987, researchers had already begun to suspect that fat was not just a simple warehouse for storing excess energy, but a metabolically active tissue secreting a variety of enzymes and hormones that regulate the processing of sugars and fatty acids. Perhaps, I thought, the lipid component of the pancreas might itself provide some additional effect, a complement to the proteolytic activity. So as a first order of business, I decided to search for an enzyme preparation containing significant fat.

Ezra Levin also assumed that the more active the product the better, the mantra Kelley again professed to me with total conviction. But I knew from my exhaustive evaluation of Kelley's files that as he opted for a more potent enzyme formulation, his response rate fell. In frustration, he assumed he only needed to prescribe an even stronger enzyme, or change encapsulators, etc, instead of retracing his steps and going backward to the less active 4× enzymes he had earlier used with great success.

I became convinced that as brilliant as Kelley had been in his prime, he had erred in his later years by assuming that "purer and more active" is always unquestionably better. I suspected that the fat-depleted, highly activated supplements may have been prone to deteriorate once encapsulated, susceptible to rapid autodigestion on the shelf. I also became convinced that the fat in the gland might not only help stabilize the mix, but provide synergistic factors to assist the proteolytic enzymes in their fight against malignant cells. Finally, I came to believe that an enzyme with less activity, with more of the total potential as precursor, might not only be more stable in the bottle, but more effective against cancer.

As a first order of business, I obtained samples of pancreatin from a number of suppliers who manufactured their own products. I also visited several health food stores and nutritional pharmacies in Manhattan, such as Willner Chemists, purchasing a variety of pancreatic enzyme supplements. In the kitchen of my mother's home in Queens where we were staying at the time, I set up my own enzyme assay, using Knox gelatin as my protein substrate instead of casein, and the Viobin preparation Viokase as my standard by which to measure the activity of other products. I dissolved each capsule or tablet in a slightly alkaline solution to help promote the enzymatic reactions and then observed the amount of gelatin digested over time. The assay, which I repeated many times for a number of weeks, worked quite well. Unfortunately, nearly all of the enzymes I tested seemed highly activated and highly processed, with all the fat removed.

Finally, I learned of the pancreas enzyme product derived from New Zealand pigs available from Allergy Research Group, a nutritional supplement company of some renown based in northern California. As a start, I was happy about the source, because I had learned that New Zealand had perhaps the cleanest environment of any country on earth, as well as the strictest laws for raising animals for commercial use. Diseases such as hoof and mouth disease and trichinosis, I was told, had never been reported there.

I also wanted enzymes derived from the pig pancreas, thought to be most similar to the human organ. For decades, before the advent of genetically engineered preparations, physicians treated their diabetic patients with pig insulin, which proved to be quite similar in terms of amino acid structure to the human variety. In a similar manner, pig enzymes, I had learned from conversations with Viobin scientists, most closely resembled ours, of all commercially available sources.

Most important, the Allergy Research Group (ARG) specifications described their pancreas supplement as a freeze-dried product, minimally processed, *with the fat intact*, yet it still tested active at moderate levels by my own assay—exactly what we wanted. Though the material had not been intentionally activated as per Levin, I suspected during the handling of the glands, some of the precursors spontaneously converted, fortuitously to the precise level we thought ideal. Then, with freeze-drying complete, all activation would come to a halt, leaving a stable product with most of the proteolytic enzymes in the precursor form.

I contacted the founder of ARG, Dr Stephen Levine, and introduced myself, explaining my plan to open up a practice and my need for good quality enzymes. Though I was

virtually unknown at the time, he agreed to provide me with as much of the product as we required. With a supply of enzymes guaranteed, in late 1987 we opened our practice with great optimism in an office in Manhattan. To our relief, this enzyme worked quite well, confirming my belief that a minimally processed lightly activated preparation, with the fat intact, was ideal for our purposes.

One of my first successes dated from December 1987, shortly after I had opened my practice in New York. A woman came to me with a diagnosis of aggressive inflammatory breast cancer that had metastasized to her bones while she was receiving chemotherapy. She had been first diagnosed in 1985 with a tumor so large she could not initially proceed with surgery. After 5 weeks of radiation to the breast to shrink the mass, she underwent mastectomy. Even after radiation, the tumor was still huge at 8 cm in widest diameter, and 17 of 17 axillary lymph nodes were involved with cancer, though there was no evidence of distant spread by radiographic studies. She then began chemotherapy with cyclophosphamide, methotrexate, and fluorouracil, which her doctors told her she would need to continue for the rest of her life, explaining that at some point the disease inevitably would recur. Unfortunately, after 2 years of treatment, in late 1987 a bone scan revealed multiple areas of activity consistent with widespread metastatic disease. At that point she consulted me, began the program with great dedication, and clinically improved. She refused any follow-up testing until some 14 years after she had begun treatment with me, when in 2001 a bone scan revealed total resolution of her disease. Today, more than 26 years from her diagnosis of metastatic inflammatory breast cancer, she remains alive, well, and cancer-free, still ingesting a fair amount of pancreatic enzymes.

We treated all our early successes, right up until 1995, with pancreatic enzymes available from ARG. Between 1995 and 1998, we entered into a research and development arrangement with Procter & Gamble, who generously provided extensive financial support as well as a team of scientists to help us determine definitively the best enzyme formulation for our purposes. The company spent considerable time, effort, and money evaluating our enzymes, even sending researchers to New Zealand to observe firsthand the entire processing of the pancreas glands from slaughterhouse to finished material. With such assistance, we eventually refined the methodology still further to help guarantee consistent manufacture of a stable, modestly active, minimally processed product with most of the enzymes—but not all—in the precursor form, and with a certain percentage of fat remaining. Working with our New Zealand supplier, we developed a method to help assure the desired potency with each batch, without the need for Levin's complicated system of fat extraction and vacuum distillation. Today, we still rely on that same enzyme preparation, which we find works even more effectively than our earlier supplement.

ORAL VERSUS INJECTABLE ENZYMES

In his 1897 text *Collected Contributions on Digestion and Diet*, Dr William Roberts reported his experiments "proving" that hydrochloric acid permanently inactivated pancreatic "ferments," as he called the enzymes, taken by mouth.[18] Beard knew of Roberts's writings, which he held in some esteem, even referencing him by name in his own book *The Enzyme Treatment of Cancer*.[12] Fully accepting Roberts's conclusions, Beard insisted that for any effect against cancer, the practitioner must administer the pancreas enzymes in an injectable form. Though Beard's proponents such as Dr Rice did prescribe oral preparations along with the injectable, these were intended strictly as supplemental, not as primary therapy.[14]

Today, 100 years later, most physiologists still cite the same mantra proposed by Roberts, claiming that pancreatic enzymes ingested orally cannot survive contact with hydrochloric acid in the stomach or autodigestion in the duodenum, nor could they ever be absorbed. Critics of our work proclaim that even if pancreatic enzymes do have an anticancer potential, our therapy as administered today can't possibly succeed because we prescribe oral formulations exclusively. When I lecture, often at the end someone will question the feasibility of systemic benefit with the oral supplements we recommend.

With all due respect to Dr Beard, physiologists, and critics, orally ingested pancreatic enzymes must survive digestive assault and be absorbed because in practice they work, as Kelley's successes and our own would attest. But if we put aside Kelley's experience or ours for a moment, a review of the scientific literature does not support the current dogma but long ago confirmed that pancreatic enzymes taken by mouth survive the gauntlet of the digestive tract and can be absorbed into the systemic circulation to a substantial degree.

The late physician Dr Edward Howell first investigated in some depth the absorption of orally ingested enzymes for possible therapeutic action during the first half of the 20th century. Howell was not an academic scientist but a practicing physician and independent researcher, best known as the grandfather of the current raw foods movement. Howell proposed decades ago that raw foodstuffs provide all the vitamins, minerals, trace elements, fibers, proteins, fats, and carbohydrates in an undamaged, optimal form allowing for greatest physiological benefit. Among these essentials, he also included enzymes present in our food, which he believed could be absorbed intact and active like a vitamin or mineral, to aid in normal metabolism and in repair of tissue damage.

In his clinical practice, Howell applied a variety of raw foods diets and enzyme supplements, claiming great success. Judging by his writings, he became rather expert not only in dietetics but in the field of enzymes, their therapeutic use, and in particular their absorption when taken by mouth. In his 1946 book, *The Status of Food Enzymes in Digestion and Metabolism*, later reprinted as *Food Enzymes for Health & Longevity*,[30] he reviewed the literature on enzyme therapeutics to that time. Surprisingly enough, he seems to have been totally ignorant of Dr Beard's thesis from 40 years earlier.

Despite that oversight, in a chapter entitled "Intestinal Absorbability of Enzymes," Dr Howell argued the case from the scientific literature that pancreatic enzymes specifically ingested as supplements survive digestion to be absorbed from the intestinal tract into both the bloodstream as well as the lymphatic system.[30]

His well-referenced document, though old, makes interesting reading from a historical perspective. When I first studied the book, I was surprised to learn that even by 1946, a considerable body of evidence indicated large proteins in general, and pancreatic enzymes in particular, taken by mouth did end up in the general circulation. In the following, Howell discussed the findings from a group of Japanese researchers who evaluated the levels of enzymes in urine over a 24-hour period after an oral challenge:

> What I believe is one of the most outstanding researches so far recorded on the fate of enzymes when taken orally was undertaken by Masumizu, Medical Clinic, Tohoku Imperial University, Japan. Masumizu's work is remarkable in several ways. The experiments were conducted, not upon isolated specimens of urine, but upon the complete 24 hour excretion, thereby insuring the presence of all enzymes excreted, instead of only a portion. The experimental animals, 10 rabbits, were given by os [mouth], 5 grams of pancreatin or 5 grams of fungus amylase for each rabbit per day. Since this dosage is comparatively enormous for small animals, the experiments prove beyond doubt that even large quantities of enzymes can be absorbed and find their way into the urine.[30]

In more recent times, the published literature again confirms that orally ingested enzymes can survive exposure to hydrochloric acid in the stomach, the alkaline environment of the duodenum, and be absorbed efficiently through the small intestinal mucosa.

We will address the first point, the denaturation of pancreatic enzymes by stomach acid. An article by Moskvichyov et al[31] of the All-Union Scientific Research Technological Institute of Antibiotics and Enzymes for Medical Applications, published in *Enzyme Microbiology and Technology* in 1988, discussed this very issue in some detail. The authors begin by reviewing the previously published data, which rather conclusively demonstrated the stability of trypsin exposed to high temperatures even in the presence of acid:

> In the first reports by J.H. Northrop, J. Mellanby and V.J. Woolley on heating trypsin in dilute acid solutions up to boiling point it was demonstrated that activity loss was minimal. The unusual property of trypsin, i.e. its high thermostability, was not clearly understood then. The most interesting and promising reports did not appear until the late 1960s, when the kinetics of the reverse denaturation of trypsin and chymotrypsin were described. It was then established that the unusual properties of these proteinases are due to the conformational transitions between different states of the protein molecule while the equilibrium between them may shift, depending upon external conditions.[31]

Moskvichyov et al[31] describe their own elaborate experiments proving stability of trypsin even when exposed to acid at high temperatures. The authors demonstrated that in a solution of heated acid, active trypsin exists in a dynamic equilibrium with its denatured configuration. With higher heat and greater acid concentration, the reaction favors the denatured form; with cooling and a more alkaline pH, the process yields more of the active trypsin. In this system, the inactive conformation, apparently protected from damage, can convert, as pH goes up and temperature drops, back into the functional enzyme. This work proves that trypsin denaturation by heat or acid is *not permanent but a reversible process*—thus contradicting the basic assumptions of many.

Therefore, orally ingested pancreatic enzyme preparations should easily survive the hydrochloric acid present in the stomach. In the next assumed obstacle, the alkaline liquid environment of the duodenum, the enzymes become most active—and most susceptible, the experts teach, to autodigestion. Few of these molecules, they claim, could possibly survive this drive to mass molecular suicide.

Once again, contrary to tradition, the evidence shows that pancreatic enzymes including trypsin, lipase, and amylase survive the duodenal environment largely intact and active. In a 1975 study, Legg and Spencer[32] reported their experiences with the 3 enzymes stored for 4 weeks in alkaline human duodenal juice at various temperatures. All 3 seemed fairly stable kept at -20°C, with 85% of the trypsin retained in its active state. At 5°C, 70% of the trypsin remained potent. At room temperature, losses were more substantial, though even after 4 days, 70% of trypsin remained viable, a rather substantial amount. Clearly, pancreatic enzymes appear stable in duodenal juices, even at room temperature, even for a considerable period of time.

Contemporary critics have long proclaimed the third obstacle, the improbable absorption of pancreatic enzymes through the intestinal mucosa, as the most daunting, in their minds precluding any systemic benefit from orally ingested preparations. In the standard teaching, with each meal the pancreas must pour out a substantial quantity of newly minted enzymes, which will gradually digest themselves away along with the food. This scenario requires that the gland must continually synthesize enormous amounts of all enzymes in constant preparation for the next meal, 24 hours a day, for the lifetime of the organism.[33]

Yet again, the actual scientific data contradict cherished traditions. Over the past 3 decades, the physiologists Charles Liebow, currently at the State University of New York at Buffalo, and who taught at Cornell Medical College during my days there, and Stephen Rothman, of the University of California, San Francisco, have investigated the absorption of activated pancreatic enzymes as well as their precursors.

In their long years of research, these 2 investigators focused on the recycling of pancreatic enzymes secreted into the intestinal tract during digestion. As their first premise, they thought it impossible that the pancreas could create the copious enzyme supply needed for each meal de novo as

experts have long assumed. In a series of elegant experiments they demonstrated that contrary to accepted dogma, the enzyme load secreted by the pancreas during meals isn't destroyed but instead largely reabsorbed and recycled, in what they refer to as an "enteropancreatic" process, akin to the enterohepatic recirculation of bile salts.

In an early article on the subject entitled "Enteropancreatic Circulation of Digestive Enzymes," published in *Science* in 1975, Liebow and Rothman[34] reported on the absorption of enzymes both in laboratory models as well as in live animals. They conclude that the enzymes easily pass through the intestinal mucosa:

> Digestive enzyme in the blood can be derived from at least two sources—the acinar cell itself and from the intestinal lumen via the bloodstream. The intestinal epithelium is permeable to a variety of proteins; for digestive enzymes in particular, substantial elastase, chymotrypsin, and trypsin permeabilities have been reported. We examined chymotrypsinogen permeability by comparing the mucosal to serosal flux of [^{3}H]chymotrypsinogen relative to that for [^{131}I] albumin across gut sacs prepared from rabbit ileum … nevertheless, we found that the permeability of the ileal membrane to chymotrypsinogen expressed per unit of concentration gradient was some nine times greater than that found for albumin …
>
> The existence of an enteropancreatic circulation for at least some digestive enzymes seems clear.[34]

Not surprising, their initial findings met with strong resistance from fellow physiologists, who despite the formidable evidence stuck to the old belief that pancreatic enzymes cannot be absorbed through the intestinal lining. To their credit, Liebow and Rothman[33] continued their studies, eventually summarizing their experience as well as the controversy still lingering over their findings in a lengthy review article entitled "Conservation of Digestive Enzymes" appearing in the January 2002 issue of *Physiology Reviews*. Their article begins:

> In this review we summarize experiments whose implications were of great interest when they were first reported. They provided unexpected evidence that the conventional belief that every meal is digested by an entirely new complement of digestive enzymes is incorrect. The data suggested that instead of being completely degraded in the small bowel with the food they digest, a large fraction of the digestive enzymes secreted by the pancreas are absorbed and recycled in an enteropancreatic circulation.[33]

The authors then proceed to catalogue in some detail the results of their experiments over the years, before essentially demolishing their critics. After some 16 pages, they conclude:

> As we reexamined the evidence for a conservation of digestive enzymes, we found it no less compelling than we did 25 years ago. Likewise, we found the studies that question its existence as incomplete as they seemed to us all those years ago …
>
> The traditional single pass view of digestion in which a completely new complement of digestive enzymes is manufactured for each meal has the curious consequence of requiring the organism to be particularly wasteful in its expenditure of energy to manufacture these costly molecules to meet its needs for sustenance … when just the opposite would seem desirable.[33]

Liebow and Rothman thus show that pancreatic enzymes present in the small intestine don't self-destruct but survive to be largely and efficiently assimilated into the bloodstream for reuse. Though the 2 researchers have specifically studied the fate of enzymes secreted into the duodenum by the pancreas, the same rule presumably holds true for enzymes provided in supplement form.

To summarize, orally ingested pancreatic enzymes may easily survive the alleged ravages of hydrochloric acid in the stomach, the alkaline environment of the duodenum, and can then pass into the systemic circulation, with little loss along the way. The scientific documentation as reported in the literature therefore suggests that oral preparations can have a systemic effect as we have witnessed in our practice for some 27 years.

As a final point, I had observed, in my review of Kelley's patient charts, that a modestly activated product with most of the enzymes in precursor form worked best. In our own practice beginning in 1987, we found such a formulation seemed to work quite efficiently, though we weren't sure on a molecular level why this might be the case, particularly because Kelley had strongly argued for a highly activated supplement. It wasn't until we became aware, in 2005, of the research of Novak and Trnka[35] that we finally discovered a rationale for our less activated product. In their excellent article "Proenzyme Therapy of Cancer," the authors, very much aware of Dr Beard's work, surmise that the injectable formulations he recommended for treatment unbeknownst to him most likely provided a high percentage of precursors.[35] The authors point out that Beard always insisted that for best results, the pancreatin must be prepared from fresh animal glands quickly processed, material that would provide most of the enzymes in their inactive conformation. Though Beard always identified trypsin as the primary anticancer enzyme, Novak and Trnka insist the proenzymes such as trypsinogen and not the active configurations provided benefit in Beard's investigations.

In their own animal and human studies, Novak and Trnka[35] discovered that a pancreatin consisting mostly of precursors and not active enzymes worked best against cancer. Active pancreatic proteases present in the systemic circulation, as a start, appear susceptible to neutralization by a series of enzyme-blocking molecules called serpins present in blood. On the other hand, the proenzymes seem completely immune to such assault. Subsequently, at the cancer cell membrane—but not in normal tissues—the precursors

quickly convert into their active conformation capable of attacking the malignant tissue directly and effectively. As they write in their abstract:

> We hypothesize that the provision of zymogens [proenzymes], rather than the enzymes, was of crucial importance to the clinical effectiveness in the human trials conducted by Beard and his co-workers. The precursor nature of the active enzymes may offer protection against numerous serpins present in the tissues and blood. Experimental evidence supports the assertion that the conversion from proenzyme to enzyme occurs selectively on the surface of the tumor cells, but not on normal cells. We believe that this selectivity of activation is responsible for the antitumor/antimetastatic effect of proenzyme therapy and low toxicity to normal cells or tumor host. …These findings support the conclusion that proteolysis is the active mechanism of the proenzyme treatment.[35]

Though Novak and Trnka used only injectable enzymes in their studies, we believe the same rule applies to our orally ingested, largely unpurified, predominantly precursor product. We suspect a high percentage of the proenzymes do not undergo activation in their journey through the stomach and duodenum but remain in their inactive form to be absorbed as such. Then, after circulating unaffected by the various enzyme blockers in the blood, at the cancer cell membrane the precursors unleash a potent anticancer effect.

TWO CASES

In an article about our treatment approach appearing in the January/February 2007 issue of *Alternative Therapies,* I presented 6 unusual cases of patients diagnosed with poor prognosis or terminal cancer who had done well for prolonged periods on their nutritional regimen.[36] A lengthier version of the article posted on the *Alternative Therapies* Web site included 36 such case reports of our successfully treated patients.

Here we provide 2 more recent cases that were not included in the first article that we believe illustrate the continued efficacy of the enzyme-based therapy.

Patient 1: A Survivor of Stage IV Lung Cancer

Patient 1 is a 62-year-old man with a past medical history significant for elevated cholesterol, hypertension, and emphysema associated with a 35-year history of cigarette smoking, though he quit in 2001.

A computer expert by training, Patient 1 had been in good health before developing cancer. Despite a tough work schedule, he exercised regularly and followed-up with his annual physical exams at Kaiser. A routine chest X-ray in August 2008 showed "minimal insignificant thickening of pleura at both apices," which was discounted as being significant. But in August of 2009, Patient 1 first experienced persistent pain in his right-lower flank, the result, he thought, of pushing his exercise routine too hard.

The pain continued to worsen, and in October 2009 when Patient 1 first noticed bright red blood in his stool, he consulted with his primary care physician, who ordered CT scans of the abdomen and pelvis. The tests showed no abnormalities in the abdomen or pelvis but did reveal a right pleural effusion. A CT scan of the chest in mid-November 2009 indicated multiple pulmonary tumors as described in the radiology report:

> … there are now evident multiple right pleural masses ranging in size from 1.5 × 4.0 cm down to 1.0 cm in the right lower chest with the largest pleural masses measuring 5.0 cm and 2.5 cm in the right pulmonary apex consistent with a Pancoast tumor. … The 4.0 × 1.5 cm mass also destroys the adjacent right 7th rib in a permeative fashion consistent with metastatic disease.[36]

Two days later, an enhanced CT scan confirmed multiple lesions in the right lung, invasion of the seventh rib, and evidence of a left adrenal mass: "The central aspect of the left adrenal gland appears as a convex contour and this is suspicious for a mass that measures 1.0 cm."[36]

A fine needle aspirate of a right pleural-based lesion confirmed squamous cell carcinoma consistent with a lung primary. At that point, Patient 1's primary care physician suggested Percocet for his persistent pain, referred him to an oncologist, and arranged for a positron emission tomography (PET) scan, which in early December 2009 revealed evidence of significant disease:

> There is a hypermetabolic density in the right upper lung involving the pleura laterally and invading the chest wall at the level of the right second (2nd) rib (with possible bony involvement) with a max SUV [activity] of 14.6 measuring 2.9 × 2.3 cm. There as another nodular hypermetabolic mass involving the pleura in the right upper lung adjacent to the right fourth (4th) rib (max SUV 11.1 measuring 2.7 × 1.9 cm). There is a conglomerate of at least three (3) pleural-based hypermetabolic densities in the right lower lobe laterally invading the pleura and right lateral eighth (8th) rib. … An additional similar pleural lesion is noted involving the anterolateral aspect of the right fifth (5th) rib …
>
> There is mild focal increased activity in the distal esophagus with a max SUV of 3.7 and mild thickening of the mucosa. There is a right retrocrural node with a max SUV of 10.8 measuring 1.9 cm.[36]

The appointment with the oncologist went ahead as planned during the second week of December 2009. To evaluate the skeletal metastases, the physician suggested a bone scan which in mid-December 2009 indicated the following: "Findings consistent with osteoblastic metastasis within the right postero lateral eight (8th) rib, correlating to recent PET/CT findings. There is no evidence of osteoblastic metastatic disease elsewhere …"[36]

With the workup completed, Patient 1 met again with his oncologist who explained that due to the extent of his metastatic disease surgery was not an option. Instead, he recommended aggressive chemotherapy with Taxol and

carboplatin to begin as soon as possible, though according to Patient 1 he acknowledged the treatment at best would only be palliative, not curative, perhaps extending his life several months. With this information in hand and his disease considered incurable, Patient 1 decided against proceeding with conventional approaches. When asked, his oncologist admitted that without any treatment, he might live 6 months.

At that point, his doctors referred him for palliative care and to a staff acupuncturist for pain control. Patient 1 then went on a crash course of self-education about alternative approaches. He changed his diet radically, cut out junk food and refined carbohydrates, and began juicing and eating a largely plant-based 100% organic diet. He stopped the Zocor and Cozaar he had been taking for his high cholesterol and hypertension. Then in late December 2009, through a mutual friend, Patient 1 learned about my regimen, contacted our office, and because his attitude seemed so determined despite his situation we agreed to take him on as a patient.

I met with Patient 1 for the first time in mid-January 2010. He reported that his rapidly worsening fatigue had cut into his professional life, to the point he now could work no more than 4 hours a day before exhaustion would set in. In addition, he described severe right flank pain. He hadn't been taking the recommended analgesics because of side effects but was continuing with the acupuncture treatments, which he found somewhat helpful. I suggested that at least for now he continue the Percocet.

Thereafter, Patient 1 adjusted to the program well, though his pain at times could be unbearable even with Percocet. But gradually, Patient 1 began to improve. By April 2010, after only 2 months on treatment, he reported in a phone conversation that "the terrible bone pain" had completely resolved, so much so that he had been able to discontinue Percocet. He told me he felt great, and friends thought he looked "great." In fact he felt well enough to begin a vigorous exercise program at a local gym. A recent series of pulmonary function tests, according to Patient 1, were "perfect." And his blood pressure, off all medication, came in at 117/77.

I then saw Patient 1 and his wife in my office for his scheduled lengthy 6-month follow-up visit during the third week of July 2010. He looked, as my note from the session described, "wonderful," and he again reported feeling "great." He described his energy as "great" and stamina as "great," and he was sleeping well and could now work a full 8-hour day without difficulty. He reported that a recent cholesterol test at Kaiser was normal. I made some adjustments in his protocol at the time, and once back home, he continued with the same dedication to the therapy as before.

Thereafter, Patient 1 continued doing well. A year after his first visit with me, during the third week of January 2011, he developed severe right back pain in the area of his metastatic rib lesion. He faxed me a note reporting that the pain was quite severe and when we spoke by phone I didn't like the sound of what he was telling me and insisted he needed a CT scan as soon as possible. That same day, CT studies of the chest and abdomen, his first since his initial workup in the fall of 2009, demonstrated pulmonary emboli in both lungs but no evidence of the multiple pleural-based tumors noted on the CT from November 10, 2009. A CT scan of the abdomen did reveal several small lesions in the liver, though the left adrenal mass seen on the enhanced CT scan from November 13, 2009 was not evident: "There are small hypodensities beneath the anterior liver capsule and the dome of the liver suggestive of early metastases. The spleen, gallbladder, pancreas, adrenal glands are normal …"[36]

With the diagnosis confirmed, Patient 1 was immediately started on Lovenox and Coumadin. The following day, ultrasound studies of his lower extremities revealed "an occlusive thrombus involving the right peroneal vein."[36]

With Patient 1 now stabilized, we had a long talk about the recent events. He said his doctors were dumbfounded that the lungs as well as the ribs showed no evidence of cancer whatsoever. Multiple radiologists had reviewed the scans, and there apparently was so much disbelief about the situation they had pulled out the original films to compare and re-evaluate. Indeed, despite their doubts, the multiple right lung tumors clearly seen in November 2009 were gone. And these had not been small tumors; the largest had measured 5 cm in widest diameter.

As for the small lesions now noted in the liver, the reports of the CT scan of the abdomen from late November 2009 and the PET scan from early December 2009 had not indicated any abnormalities in the liver. Patient 1 didn't start his nutritional regimen until late January 2010, some 7 weeks after the PET scan. Because his disease was so aggressive, I suspected that during the time between the original CT and PET studies in November and early December 2009 and the time he started his therapy in late January 2010, his cancer would have continued to spread.

We also discussed the blood clots in some detail. As it turned out, I didn't know the whole story when he had first called complaining of back pain. Just before he developed the backaches in the third week of January 2011, he had driven 12 hours nonstop to visit relatives in the midwest—a trip he hadn't discussed with me, assuming I would tell him not to do it. After several days with family, he then drove 12 hours back, again nonstop. I thought the clots easily could have developed during the long drives.

During the second week of February 2011, Patient 1's primary care physician arranged for an abdominal ultrasound to re-examine the liver lesions. The doctor's note to Patient 1 about results indicated the nodules seen on the January CT scan were gone: "Your ultrasound: No abnormal hepatic masses visualized."

I next saw him in my office in late July 2011, 18 months after his diagnosis, at which time he reported excellent energy, stamina, and concentration. His various pains remained completely resolved and he had resumed working 10- to 14-hour days without any drop in his energy. I advised him that he had to pace himself more reasonably and not try to conquer the world.

Today, in October 2014, nearly 5 years from his diagnosis, Patient 1 feels "great," with no evidence of his once widely metastatic disease.

Squamous cell carcinoma is one of the more aggressive of lung cancers, with fewer than 5% of those diagnosed at stage IV, as in the case of Patient 1, surviving 5 years. Considering the extent of his disease when initially diagnosed, Patient 1's current survival of nearly 5 years is unusual, particularly since he enjoys such excellent health. On his nutritional program his debilitating pain has completely resolved, his blood pressure and cholesterol have normalized without drugs, his energy is superb, and he continues his productive, creative life. Further, the regression of all his extensive lung and bone lesions after 1 year of treatment, and the subsequent resolution of his liver disease, certainly indicates a good response to therapy.

Patient #2: A Survivor of Burkitt's Lymphoma

Patient 2 is a 39-year-old woman with a diagnosis of Burkitt's lymphoma that failed to go into remission with chemotherapy, who has now survived 5.5 years on her nutritional regimen.

In terms of her family history, at least 7 of Patient 2's close relatives had been diagnosed with cancer, including her father with prostate cancer, a sister with cervical and skin cancer, a grandfather who died of leukemia, a grandmother who died from colon cancer, an uncle who died of lung cancer at a young age, a first cousin who died of colon cancer, and another first cousin with metastatic colon cancer.

Prior to developing lymphoma, Patient 2 had a distant history of allergies that developed when she was 10 years old and that her parents, with a long interest in nutrition, treated effectively with a whole foods organic diet and a variety of nutritional supplements. Thereafter, she did quite well, and throughout her 20s, she remained vigilant with her diet and health habits while also pursuing athletic and outdoor activities.

Patient 2 had been in her usual state of good health when in March 2008, she first experienced persistent low back pain associated with onset of drenching night sweats, diminished appetite, and weight loss of 10 pounds over a several-month period. During this time, she repeatedly consulted her family physician, who generally seemed unconcerned, though at one point he prescribed Valtrex when the patient herself suggested her symptoms might be due to shingles. However, the symptoms continued to worsen throughout late spring and early summer of 2008.

In early August 2008, over a period of several days, she developed a large mass "one-half the size of a football" in her lower back. At that point, Patient 2 was referred to a local oncologist in Washington State where she lived at the time. A CT scan in mid-August 2008 revealed an anterior mediastinal mass measuring 7.1 × 10.8 × 10.1 cm, compressing both the main pulmonary artery and aorta, and a mass adjacent to the spinal cord 5.7 × 7.4 × 7.4 cm invading the posterior chest wall and thought to be the cause of her back pain.

Two days later, a bone marrow biopsy was negative, but a CT-guided fine needle aspirate of the anterior mediastinal mass confirmed a B-cell lymphoma, positive for the CD20 antigen. Further molecular biology studies revealed a rearrangement of the c-Myc oncogene, which regulates cell division, via a translocation of chromosomes 8 and 14, or t(8:14). This finding helped confirm a diagnosis of Burkitt's lymphoma, a malignancy associated with Epstein-Barr infection, and rare in the United States though common in Africa.

By the time she was admitted to Providence St Peter's Hospital only several days after her biopsy, her clinical status was declining rapidly. A PET/CT scan at the time revealed the tumors had grown considerably in a week, the anterior mediastinal mass now measuring 15 cm, and the right paraspinal mass measuring 11 cm. In addition the PET revealed a new active 2.5 × 3.6 cm left ovarian mass and a 1.8 cm mass within the small bowel all consistent with metastatic lymphoma.

Patient 2's oncologist warned her that due to the extremely aggressive nature of her disease, she needed to begin chemotherapy immediately or she could be dead within 10 days. With no other immediate option, Patient 2 agreed to the treatment, the intensive McGrath protocol designed for patients diagnosed with Burkitt's lymphoma. The McGrath regimen consists of 2 courses, A and B, of multiagent chemotherapy given in sequence, the CODOX-M regimen A, and the IVAC regimen B. In this case, her physicians also opted to add on Rituxan, a monoclonal antibody targeting the CD20 antigen present on the membranes of certain lymphoma cells.

Only days later, Patient 2 began the McGrath A component with the drugs cyclophosphamide, doxorubicin, vincristine, methotrexate, and leucovorin rescue. Beginning on the first day of treatment, she also received Rituxan. In addition, she underwent intrathecal cytosine arabinoside (ara-C) to target any cancerous cells within the central nervous system.

After the first cycle of McGrath A, Patient 2's oncologist switched her to the McGrath regimen B (IVAC), including ifosfamide with mesna rescue, etoposide, and ara-C, which she completed in early November 2008. At that time, she also consulted with Dr Paul O'Donnell, a lymphoma expert at the Seattle Cancer Care Alliance (SCCA) at the Fred Hutchinson Cancer Research Center in Seattle to discuss treatment options. Dr O'Donnell recommended a stem-cell transplant as the only hope for long-term remission, suggesting immediate harvesting of her marrow stem cells to be kept in storage. However, he warned that for a transplant to be effective, she must enter into full remission first.

At that point, Patient 2 returned to St Peter's Hospital to complete another 2 cycles of chemotherapy. A PET scan in mid-November 2008 documented a significant response to treatment described in the radiology report:

> Complete or near complete metabolic response in the anterior mediastinal mass with marked anatomic reduction in tumor size …

> Complete metabolic response in the right lower chest lesion with near anatomic resolution.
>
> Complete metabolic response and anatomic resolution of mass in the left ovarian region and left lower quadrant bowel.

Patient 2 then returned to SCCA to complete the successful harvesting of her stem cells. Unfortunately, CT scan studies from mid-December 2008 showed that she was not yet in remission:

> Within the anterior mediastinum adjacent to the ascending aorta and main pulmonary (sic) is a heterogeneously appearing mass with calcifications measuring 5.5 × 3.0 × 2.6 cm which has not significant changed compared to the November 11 examination
>
> … The previously identified right paraspinal mass with atelectasis has decreased in size to 4 × 8 mm and now is only a small area of pleural or extrapleural thickening with a small amount of adjacent right lower lobe atelectasis.

Patient 2 eventually completed the full 6 cycles of McGrath A and B in early January 2009. But a restaging workup in late January 2009 again confirmed that Patient 2 had failed to enter remission, despite the aggressive treatment. CT scan studies of the chest, abdomen, and pelvis indicated that the anterior mediastinal mass, though somewhat reduced in size, had not completely regressed, nor had the pleural thickening and nodularity in the right lung base. A PET/CT performed the same day revealed increased activity in the mediastinum and pleura, consistent with residual malignancy:

> Heterogeneously increased activity with max SUV of 4.5 is associated with 28 × 51 mm anterior mediastinal mass. … There is increased metabolic activity with a max SUV of 3.6 associated with foci of right basal pleural nodularity and thickening. …

Further, the main tumor had increased in size when compared with an outside PET performed in November 2008.

With that bad news, in early February, Patient 2 returned to SCCA for a meeting with an oncologist assigned to her case, who bluntly stated that because she had not achieved a full remission, her chances of a successful outcome with transplant were no more than 20%, with a significant possibility of death from the arduous treatment. According to Patient 2, this physician did not push chemotherapy because the odds of response were so poor. When her parents asked about Patient 2's prognosis, the oncologist admitted that without any further conventional treatment, she might live only 6 months.

The official oncology note from that session stated, "Therefore our interpretation is that the patient's disease is progressing under a debulking chemotherapy she received during the last few months." At that point, Patient 2 had already learned about our work from a friend and after discussing the situation with her parents decided to pursue our treatment.

When I first met with Patient 2 and her parents during the second week of February 2009, she appeared emaciated and was so weak she had to lie down on the couch in my office as I conducted my intake history. Her hair had fallen out from the chemotherapy, and she reported drenching night sweats requiring change of bed clothes 4 or 5 times nightly, chronic low grade fevers, headaches, and a persistent neuropathy, a side effect from her chemotherapy.

Despite her dire situation, Patient 2 proceeded with her nutritional therapy with great determination, great dedication, great enthusiasm, and, importantly, with full support of her parents. With all she had been through at her age, I marveled at her positive outlook and had nothing but admiration for her. She understood fully the severity of her situation but would do everything she could, she said, to "beat the odds." And within weeks of beginning the regimen, she reported a significant change in her health for the better. She felt strong enough she had begun riding a bicycle daily, telling me in a phone conversation she felt "like a million bucks."

CT scan studies performed March 31, 2009, after Patient 2 had completed only 6 weeks on her nutritional therapy, showed a significant reduction of approximately "50%," compared with the CT scan from mid-December 2008. The radiology report states:

> There has been decrease in the size of the anterior mediastinal mass which now measures 3.7 × 2 cm in transverse diameter, compared to 5.6 × 3 cm previously. There are more prominent calcifications due to treated lymphoma. There is somewhat less prominent, mild soft tissue fullness in the right paraspinal region at the T11 and T12 levels, without definite focal mass seen in this region.
>
> No significant mediastinal adenopathy or other mass are seen.

A chest X-ray ordered by her oncologist during the third week of June 2009 showed apparently near-total resolution of the mediastinal mass compared with an X-ray from early January 2009: "Impression/Decreased mild residual fullness of the left hilum and left AP window region./No acute cardiopulmonary process."

Subsequently, Patient 2 continued her program and continued doing well. All her previous serious symptoms—the anorexia, fatigue, night sweats, and weight loss—had resolved within months. In a phone conversation mid-January 2010, after she had completed nearly a year of her nutritional therapy, Patient 2 reported feeling "great." A PET/CT scan a month later, in February 2010, showed no residual or active lesions—she appeared to be in complete remission.

Subsequently, she has done very well. Although she had been warned before beginning her aggressive chemotherapy in August 2008 that the protocol would render her sterile, in March 2010 she called me to let me know she was pregnant. Throughout her pregnancy, she remained vigilant with her therapy, experienced virtually no symptoms, and in late December 2010 gave birth to a very healthy girl.

Today, 3.5 years later, both patient, now 39 years old and still on her nutritional regimen, and daughter, remain in excellent health.

I always learn much from my patients. From my first meeting with Patient 2, I was impressed with her positive manner, though she had been given a terminal prognosis, a terrible predicament for someone so young, and she was so weak during that session she couldn't sit in a chair. But her determination was evident, and her parents were both very supportive of her choosing our therapy. Patient 2 has repeatedly expressed her enormous gratitude for the therapy we make available as have her parents, who feel the treatment saved their daughter's life. Over the years, I have come to believe fully that the attitude of the patient, and the attitude of caregivers, are together the single most important determining factors between a successful outcome and failure. Patients at peace with their situation and grateful for each day, not filled with anxiety, doubt, and fear, always do the best. And supportive family and friends can make a huge difference in terms of the ultimate outcome.

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