

# Pancreatic Proteolytic Enzymes and Cancer: New Support for an Old Theory

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## Abstract

In 1905, the embryologist John Beard first proposed that pancreatic proteolytic enzymes had potential as a treatment for cancer. His theories were dismissed by the medical world a decade later, but various practitioners have kept the concept alive through the publication of case reports of cancer patients treated with pancreatic proteolytic enzymes. In the last 2 decades, studies of the role of proteases in physiology have made it clear that they do more than digest food. This article reviews the history of the clinical use of pancreatic proteolytic enzymes in cancer treatment, and recent research on protease activated receptors and their role in cancer.

## Keywords

cancer, enzymes, pancreatic enzymes, proteolytic enzymes, trophoblast, cancer stem cells, case reports, proteases, protease activated receptors, primordial germ cells

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## Content

In 1902, in an article in *The Lancet*, Beard<sup>1</sup> proposed that the answer to questions about the origin of cancer could be found in his own field, embryology. He observed that the early stage of the placenta, the trophoblast, looked and acted much like a cancer as it invaded the uterus and created a blood supply. He reported the presence of “vagrant germ cells” in the tissues of embryos far from the placenta, and suggested that these could become like invasive trophoblast cells, forming the nidus of development of cancer in the future.<sup>2,3</sup>

In normal development, trophoblast cells differ from cancer in 1 key respect. At a certain point in development—Beard claimed at 56 days in humans—the trophoblast stops invading, changing in character from a poorly differentiated, angiogenic tissue into the mature placenta. Beard looked for the signal that induced this transformation, believing that if he found it, he might also find a treatment for cancer. He reported that in a number of mammalian species, this change takes place when the fetal pancreas begins manufacturing proteolytic enzymes.<sup>4</sup> Beard<sup>5</sup> then tested his theory in a mouse model of cancer, Jensen’s mouse tumor. After injections of the commercially available pancreatic enzyme trypsin, the tumor in a treated mouse was much smaller than that in an untreated control.

Over the next several years, a number of physicians injected enzyme preparations into cancer patients, with variable success. Reviews of these cases have been published elsewhere.<sup>6,7</sup> One of Beard’s chief critics, Bainbridge, a

professor of surgery in New York City, treated a series of patients; he described the treatment as ineffective, and injected enzymes as intolerably painful.<sup>8</sup> In his 1911 book, *The Enzyme Treatment of Cancer and Its Scientific Basis*, Beard<sup>2</sup> reviewed these successes and failures, and bemoaned the wide variation in the quality of available enzymes that he believed explained why sometimes the treatment was unsuccessful. He rebutted Bainbridge vigorously, stating that on review of Bainbridge’s cases, many were clearly too ill to benefit, had previously been treated with surgery and radiation that would handicap their ability to respond, and that the doses of enzymes administered were too weak. Then in 1914, Bainbridge<sup>9</sup> published a popular book, *The Cancer Problem*, in which he reiterated his opinion of enzyme treatment. By the time Beard died in 1924, interest in his work had gradually trickled away.

## Clinical Results With Pancreatic Proteolytic Enzymes

However, over the following years, other physicians implemented cancer treatment with proteolytic enzymes. In a

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1928 letter, May<sup>10</sup> reported some benefit for his cancer patients with an extract of pancreas he prepared himself, while a commercial powdered preparation had no effect. And in 1934, Morse presented case reports to the St. Louis Medical Society of cancer patients treated with trypsin; the session description does not include details of the patient histories.<sup>11</sup>

After learning of Beard's theories, in the 1950s and 1960s, Shively administered trypsin, chymotrypsin, ribonuclease, desoxyribonuclease, and pepsinogen intravenously to cancer patients.<sup>12</sup> He used crystallized enzymes, purified by the methods available at the time, but most likely containing additional pancreatic proteins.<sup>13</sup> He also used amylase, at first intravenously, then orally.

In 1964, the Food and Drug Administration outlawed intravenous and injectable enzymes, so Shively stopped his work, turned his research notes into a book, *Multiple Proteolytic Enzyme Therapy of Cancer*, and sent copies free of charge to medical libraries throughout the United States.<sup>14</sup> A brief summary of his results is available elsewhere.<sup>15</sup> Many of the cases in the book are difficult to assess because of the limited diagnostic tools in that era, short follow-up, and complicated treatment courses including other modalities such as radiation. Shively described multiple examples of clinical improvement, such as resolution of palpable masses and malignant fluid collections. In some of the cases, after an initial success, when the disease recurred, the patient tried something else rather than resuming the enzyme treatment, suggesting neither Shively nor the patient understood that maintenance therapy might be needed.

Around the same time, Kelley, an orthodontist by training, began treating cancer patients with oral pancreatin. Kelley created his nutritional program first for himself, in desperation after his doctors told him he had terminal cancer, based on weight loss and a palpable mass. He never had a formal tissue diagnosis, not unusual in the era prior to scans and needle biopsies, so the diagnosis was never confirmed.

Kelley's protocol included dietary modification and coffee enemas, as well as large amounts of oral pancreatin. After he regained his health, others with cancer sought him out, and his practice gradually migrated from orthodontics to controversial cancer treatment.

In the early 1980s, Gonzalez<sup>16</sup> embarked on a multi-year review of Kelley's methods and records, as detailed in his book *One Man Alone*. Gonzalez found that a number of patients in Kelley's practice had appropriately diagnosed cancer and were still alive years after they should have expired, far too many to be explained away as spontaneous remissions.<sup>17</sup> He included 50 such cases in his monograph. Gonzalez also investigated outcomes for all patients with pancreatic cancer seen by Kelley from 1974 to 1982, dividing them into groups based on adherence. Those who never

followed Kelley's protocol had a mean survival of 2 months; those who followed it partially, 10 months; and those who followed it completely, 8 years, with some still alive at the end of the project.<sup>16</sup>

After completing his review, Gonzalez set out to recreate Kelley's methodology in the hopes of proceeding with more formal clinical testing. Gonzalez presented 25 "best cases" from his own practice to the National Cancer Center in 1993, after only 6 years in practice.<sup>18,19</sup> Subsequently, Gonzalez and Isaacs<sup>20</sup> published the results of a pilot study with 11 patients suffering from pancreatic cancer, showing an 81% survival at 1 year and a 45% survival at 2 years, well above the usual statistics for this particularly dismal cancer.

A follow-up trial directly comparing this enzyme-based nutritional program to gemcitabine-based chemotherapy, administered through one of the major medical centers in New York City, unfortunately did not demonstrate similar results. The trial was originally to be a randomized trial, but due to poor accrual, was changed to a patient choice trial.<sup>21</sup> The patients were screened and admitted to the chemotherapy arm or the nutritional arm by the scientists at the academic center. Those on the nutritional arm were seen by Gonzalez or Isaacs, but they also saw local physicians, usually oncologists, for monthly physical exams and bloodwork.

There was considerable contention as the study went along about whether the patients assigned to the nutritional arm actually adhered to the protocol. In a book about the clinical trial, Gonzalez<sup>22</sup> claimed that out of the 39 patients assigned to the nutritional arm of the study, 16 (41%) had discontinued the treatment within 1 month of study accrual, for reasons varying from opposition from family or physicians, to an inability to eat and swallow the supplements. Ability to eat 3 meals a day was an entrance criterion; 1 patient was hospitalized within a week of study entry due to inability to keep down water. To quote a letter written by a representative of the governmental funding agency after a meeting:

We discussed at considerable length his [Gonzalez's] concerns about the probable accrual of patients unable to comply fully with the nutrition arm of the protocol. It was our impression that everyone in the room basically agreed that, despite best efforts, there is in fact, reason to be concerned about this issue, and that it clouds interpretation of the data.<sup>23</sup>

The published results of the trial stated that patients treated with gemcitabine-based chemotherapy survived 3 times as long (14.0 vs 4.3 months) and had better quality of life than those who chose proteolytic enzyme treatment.<sup>24</sup> The known issues with adherence were not discussed in the article.

Gonzalez and Isaacs's treatment, based on Kelley's previous work, involves extensive dietary and lifestyle modification in addition to pancreatic proteolytic enzymes,

and some believe that it is too difficult for most patients to follow. Isaacs argued in her critique of the study design and implementation that better support of the patients' lifestyle change, and less opposition from other physicians, would have improved adherence.<sup>21</sup>

Subsequent publications by Gonzalez and Isaacs about this enzyme-based nutritional method have included more than 100 case reports, discussing patients with lengthy and in many cases, continuing survival.<sup>6,25-27</sup> A collection of case reports published in 2007 included a patient who had applied and been refused admission to the clinical trial mentioned above. In December 2000, computed tomography showed a 3.4 cm mass in the head of the pancreas; biopsy February 2001 demonstrated poorly differentiated adenocarcinoma. The pathology slides were then sent to the Mayo Clinic, where the diagnosis was confirmed. She was denied entry to the clinical trial because her disease was considered resectable, though she had refused surgery multiple times. She then embarked on the enzyme-based nutritional protocol outside of the clinical trial. She has now survived more than 20 years since biopsy. She has never received surgery, chemotherapy, or radiation.

The 2 most recently published case reports illustrate the importance of adherence.<sup>28</sup> The first patient was diagnosed with colon cancer that was resected May 2014. After his carcinoembryonic antigen began to rise, he began chemotherapy in early 2015. A new liver lesion developed in June 2015, and he stopped chemotherapy. After further growth, the liver lesion was removed in February 2016 and confirmed to be metastatic colon cancer, extending to the margin of resection. He subsequently began an enzyme-based nutritional program in April 2016. A scan 2 months later showed regrowth of the liver lesion and a new pulmonary mass. The liver lesion was resected in July 2016 and reported to be "Metastatic nodule of colorectal-type adenocarcinoma with no residual viable tumor identified." Since then, the patient has had no treatment besides his nutritional program. On subsequent scans, the pulmonary lesion gradually disappeared, to the astonishment of his oncologist. At last contact December 2021, he was alive and well, working at a demanding job while also continuing his treatment protocol. Recent scans of the thorax and abdomen showed no sign of disease.

The second patient developed neurological symptoms leading to the discovery of masses in his lung and brain in February 2014. The brain mass was resected and found to be metastatic adenocarcinoma, most likely non-small cell lung cancer. He received radiation to the brain, then embarked on a self-designed nutritional program. With this, his lung masses enlarged and he developed recurrent brain lesions.

In January 2015, he began the enzyme-based nutritional program, but he also underwent more radiation to the brain due to concerns about incipient herniation. In August 2015,

scans showed resolution of the pulmonary masses previously seen, and stable findings in the brain. He never had radiation targeting his lung, or systemic therapy.

He did well until June 2018, when he developed focal seizures and weakness. Scans of the chest showed no evidence of disease; magnetic resonance imaging of the brain showed recent hemorrhage in the mass that had been present since radiation. His physicians concluded that he had residual radiation damage and acute clinical deterioration due to bleeding. Unfortunately, he was left with hemiparesis that made it hard for him to take care of himself; he lived alone, with no outside support. He discontinued his enzyme-based nutritional program, and 2 years later his disease recurred. He died in May 2020, more than 6 years from diagnosis. In comparison, in a case series of patients with a similar initial presentation, median survival was around 9 months.<sup>29</sup>

In a 2001 article, Sakalova et al<sup>30</sup> reported prolongation of life in patients with multiple myeloma treated with Wobe-Mugos E, an oral enteric-coated combination of papain, trypsin, and chymotrypsin. In this retrospective cohort study, Stage III patients who received Wobe-Mugos E in addition to chemotherapy survived 83 months, compared with 43 months in the control group who received only chemotherapy. Reviews of other studies using Wobe-Mugos have been published elsewhere.<sup>14</sup> In a 2008 article, Wald<sup>31</sup> reported positive results in mouse experimental tumor models with rectally administered enzymes in composition and proportions similar to Wobe-Mugos.

A 2017 article by Peran et al<sup>32</sup> included a series of 46 patients with a variety of malignancies who were treated with a rectal suppository made with a proenzyme combination studied. Treatment effect was assessed by comparing the overall survival of patients under treatment to the life expectancy assigned to each patient prior to treatment start. Around 19 of 46 patients reportedly survived longer than expected; however, no details of the cases are provided, and such survival estimates may not be reliable.

A 2017 retrospective analysis of patients who had received pancreatoduodenectomy for periampullary malignancy found that pancreas exocrine replacement therapy was associated with increased survival.<sup>33</sup> The authors attributed this to improved nutritional status.

## Protease Activated Receptors and Cancer

In Beard's time, pancreatic ferments, as they were called, were believed to have a role in digestion of food, and nothing more. Beard's contention that pancreatic enzymes from the developing fetus controlled the invasion of the trophoblast, and that they could also control malignant cells, fell on deaf ears during his lifetime and for many decades subsequently.

In more recent years, with the realization that proteases make up more than 2% of the human genome, protease systems have been found to be important regulators of many biological mechanisms. The 2019 article by Verhamme et al,<sup>34</sup> “Proteases: Pivot Points in Functional Proteomics,” reviews in detail the role of proteolytic enzymes in a myriad of physiological processes and diseases, including cancer. The article reviews the complex web formed by multiple proteases and protease inhibitors, and that “depending on the molecular environment and the binding partners, proteases may catalyze reactions that result in opposite physiological processes.”

Proteases play a role in the breakdown of the extracellular matrix that allows cancer to spread. The subsequent discovery of receptors on cell surfaces that are activated by proteases has stimulated further interest in the role of proteases in cancer—and in the regulation of trophoblast cells.<sup>35</sup> Protease-activated receptors (PARs) are part of the G-protein-coupled receptor (GPCR) superfamily. Multiple different proteases may activate a single PAR by cleaving different sites on the PAR’s extension outside the cell wall. This allows for multiple protease-specific signaling responses via a single PAR, depending on the activating protease. Four different PARs have been identified; PAR-1, -3, and -4 mainly interact with thrombin, PAR-2 with trypsin. Review articles on the role of PAR-1 and PAR-2 in cancer state that these receptors are present on most cancer cells, and that activation stimulates cancer cells to divide and invade.<sup>35-37</sup>

Superficially, this would appear to negate Beard’s premise, as he speculated that pancreatic enzymes work to control cancer, not to encourage spread. But there are conflicting data: in 1 study, activation of PAR-2 inhibited the proliferation of colon stem and tumor cells.<sup>38</sup> A 2017 article looked at expression of PAR-1 in biopsy specimens from human lung cancer; PAR-1 was found in the stromal cells but not on the cancer cells themselves.<sup>39</sup> And in a 2021 study, investigators reported that PAR-2 was reduced in renal cell cancer tissues and cell lines.<sup>40</sup>

The interactions of proteases and PARs are complex; PARs can be cleaved at the “canonical” site, creating 1 reaction, or at a “noncanonical” site, creating a different reaction.<sup>37,41</sup> Differences in concentration, the presence of inhibitors and other proteases, or repetitive treatments can create different effects.<sup>42,43</sup> There are also proteases capable of activating PARs that are fixed in the cell membrane, adding to the complexity of the cell environment.<sup>44</sup>

## Proenzymes Versus Activated Enzymes

Most importantly, there is reason to believe that the key components in the pancreas product used by clinicians in

Beard’s era, as well as by all the practitioners who have followed afterwards, are not the activated forms that have been used to study PARs, but rather the proenzyme forms. In their classic function in digestion, pancreatic enzymes such as trypsin and chymotrypsin are stored in the pancreas as proenzymes, trypsinogen, and chymotrypsinogen, that are then secreted into the intestinal tract and activated by enterokinase in the brush border of the intestine. In support of a wider role in physiology, trypsinogen is produced early in fetal life, well before trypsin is needed to digest food.<sup>45</sup> And, proenzyme forms of trypsin are present in the serum of healthy adults.<sup>46</sup>

In 2005, Novak and Trnka<sup>7</sup> were the first to mention the possible role of proenzymes, when they reported activity of a mixture of trypsinogen, chymotrypsinogen and amylase in cultured tumor cells and in a mouse model. Subsequently, other investigators utilizing proenzymes reported prolonged survival in mouse models of sarcoma, melanoma, ovarian cancer, and pancreatic cancer.<sup>32,47,48</sup> These articles also included promising effects of proenzymes in cancer cell cultures; another paper reported that a combination of proenzymes and amylase suppressed the epithelial-mesenchymal transition and promoted cell differentiation.<sup>49</sup>

Beard himself recommended a pancreatic extract made from freshly minced pancreas that would have contained enzymes in both their active and proenzyme forms. Shively used crystallized enzymes intravenously that were as pure as the standards of the day allowed. But subsequent studies comparing crystallized protein with liquid chromatography show that there would have been other pancreatic products contained in the materials he used, quite possibly including proenzymes.<sup>13</sup>

The oral pancreatin available to Kelley, made by the methods patented by Levin, was pancreas tissue with the water and fat removed, and the enzymes allowed to activate to a greater or lesser degree.<sup>50</sup> The product would have contained some enzymes in the proenzyme form. Gonzalez, in his review of Kelley’s methods, believed that Kelley’s best results were obtained in eras when he had used less activated pancreatin, specifically, the 4X form, which provided more than half the potential enzymatic activity in the proenzyme form.<sup>51</sup> Gonzalez and Isaacs utilized a less processed pancreas product that presumably has the vast majority of the enzymes as proenzymes.

Oral or injected pancreatic material used in humans has almost certainly contained a mixture of active and proenzyme forms, but the use of purified proenzymes in humans has been limited to a rectal suppository preparation described in the 2017 article by Peran et al.<sup>32</sup> In this study, the investigators used a rectal formulation instead of an oral one because they believed that the product would be absorbed by the rectum’s blood vessels into the circulation, thereby avoiding digestion of the enzymes in the duodenum.

## Parenteral Versus Oral Enzyme Administration

Beard and Shively both believed that pancreatic proteolytic enzymes had to be administered parenterally to be effective. Beard advocated intra-tumoral injection; Shively administered enzymes intravenously. While there are no recent reports of intravenous administration of enzymes in humans, Peran et al<sup>32</sup> reported positive results with intravenous proenzymes in an animal model of cancer. Parenteral administration could have several advantages, including avoiding losses in the gastrointestinal tract and improved delivery of the product to tumor sites. No such product is currently commercially available, so there would be substantial developmental costs.

Oral pancreatic products are available, and have been used by Kelley, Gonzalez, and Isaacs with multiple positive case reports.<sup>6,16,20,25,28</sup> The product Gonzalez and Isaacs used has also been tested in a mouse model of pancreatic cancer, administered orally, with positive results.<sup>52</sup> In the previously cited articles regarding the enzyme product Wobe-Mugos, it was taken orally.<sup>14,30</sup> This would suggest that orally administered pancreatic enzymes and proenzymes can have a systemic effect.

Some investigators have theorized that digestive enzymes are secreted into the intestine, then absorbed and recycled through the pancreas to be reutilized.<sup>53,54</sup> If this theory is correct, exogenously administered enzymes could be absorbed via the same mechanism. In 2 experiments investigating this topic, trypsin labeled with radioactive iodine was instilled into the duodenum of a human volunteer, and samples were collected from the blood shortly afterwards.<sup>55,56</sup> Heinrich et al observed that 4.3% of the administered dose was found in the blood plasma at 15 minutes, and 5% at 30 minutes; Lake-Bakaar et al described 10.8% of the administered dose at 75 minutes. Some of the radioactive label was attached to a protein the size of trypsin, suggesting that trypsin had not been broken down to constituent parts, but was still intact.

However, Bohe et al<sup>57</sup> performed a similar experiment, instilling trypsin labeled with radioactive iodine into the duodenum, and reported that all radioactive label in the plasma was in the form of free iodine. They attributed this to deiodinating mechanisms in the intestine. In Bohe et al's study, participants were fasting and had taken potassium iodide beforehand; in Lake-Bakaar et al's study, participants had eaten breakfast and taken Lugol's solution. Heinrich et al do not comment on this.

Other investigators reported that an enteropancreatic circulation of enzymes does not exist in rats, and contested the enteropancreatic theory altogether.<sup>58,59</sup> Their study involved intravenous administration of labeled amylase and the subsequent appearance of the label in all enzymes in pancreatic juice, suggesting breakdown and reutilization. Their critique

focused on the recovery of enzymes from blood to the pancreas; they did not look at whether enzymes can be absorbed intact from the intestine.

A 2004 article by Gewert et al<sup>60</sup> is frequently quoted as evidence that orally administered pancreatic enzymes are not systemically absorbed. In this experiment, pigs who had undergone pancreatectomy were given enteric coated pancreatic enzymes with their food, and no changes in blood levels of (pro)colipase and cationic trypsin(ogen) were seen. There was no radioactive labeling of the product. This study cannot answer the question of whether enzymes are absorbed. Since the product was administered with food, it may have been used for digesting that food with little to none left for systemic absorption, or the food could slow absorption to the point that any increase in levels in the blood stream would be shallow and not easily recognized. And if proteolytic enzymes have a wider role in physiology than previously believed, they would also be present in intracellular fluid. These pancreatectomized animals would have a systemic shortage of enzymes, and absorbed enzymes might move out of the bloodstream and into the tissues, again blunting any increase in levels.

A 2019 article discussing PAR signaling in the gut suggests that proteases may interact with PAR-1 and PAR-2 receptors in the intestinal tract cells to facilitate absorption of macromolecules, and that PARs impact gut permeability regulation.<sup>61</sup>

Theoretical objections to oral administration of enzyme or proenzyme products include questions about their stability when exposed to stomach acid or duodenal juices. In 1975, Legg and Spencer documented stability of 70% in trypsin stored in duodenal juice at room temperature for 4 days.<sup>62</sup> In a 1988 paper, Moskvichyov et al<sup>63</sup> demonstrated that trypsin is stable, though inactive, in acid, reverting to its active form when in an alkaline pH.

In 1965, Heizer et al<sup>64</sup> examined the stability of trypsin in acid, acid plus pepsin, or gastric juice. Trypsin was fairly stable in acid alone, but with the addition of pepsin, it was degraded when the pH went below 4. A 1913 article on the various "ferments," as the digestive enzymes were called then, states that trypsinogen is stable in acid, but rapidly destroyed if pepsin is added.<sup>65</sup>

Kelley, Gonzalez, and Isaacs all directed patients to take their pancreas product away from meals, which would potentially limit both the amount of acid and pepsin in the stomach and the time spent in the stomach. Both Wobe-Mugos and the enzymes Kelley used were enterically coated, protecting the contents from stomach acid. Gonzalez and Isaacs used a lyophilized pancreas product with the fat left intact, unlike all the other products mentioned above. Fat suppresses acid and pepsin secretion, which may protect the product from digestion in the stomach.<sup>66</sup> While no formal testing on the stability of this lyophilized product has been done, an experiment using dogs with pancreatic

insufficiency may shed some light.<sup>67</sup> Various formulations of pancreas, including raw pancreas, were given to the dogs, and the enzyme content in their intestinal tract was evaluated. Raw pancreas delivered more enzymes to the intestinal tract than the other formulations tested. The minimally processed, lyophilized product used by Gonzalez and Isaacs would be the closest available product to raw pancreas.

## Primordial Germ Cells, the Trophoblast, and Cancer Stem Cells

Beard was the first to speculate that proteases could have an effect on cancer. However, he was not the first to notice that cancer cells look and act like embryonic cells. A 2019 article by Capp,<sup>68</sup> “Cancer Stem Cells: From Historical Roots to a New Perspective,” reviews how as early as 1877, Cohnheim and other investigators speculated that “embryonic rests,” residual embryonic cells in adult tissues, give rise to cancer.

Beard believed that the specific embryonic cells responsible for cancer development were primordial germ cells, precursors to the gonads, that normally develop and migrate to the genital ridge quite early in development. Based on his study of a particular species of fish, Beard<sup>69</sup> reported that many primordial germ cells do not travel to the proper location, instead coming to rest in other tissues. He believed that later in life, such cells, still primitive in nature, might be stimulated to behave like trophoblast cells, invading neighboring tissue and creating a blood supply to stimulate further growth.<sup>2,3</sup>

On a molecular level, the mechanisms used by cancer cells and by the trophoblast to invade and create a blood supply are the same.<sup>70,71</sup> Recent review articles provide a detailed summary of various molecular aspects of trophoblast and cancer cells, and mention the possibility that study of the trophoblast could inform efforts to address cancer.<sup>72,73</sup>

Beard stated that in normal prenatal development, the signal for the maturation of the aggressive trophoblast into the non-invasive placenta was the fetal production of pancreatic enzymes, in the first trimester. Subsequent investigators have confirmed that the fetus makes pancreatic enzymes months before they would be needed in digestion.<sup>45,74</sup> Trophoblast cells have PARs, and in 1 intriguing article, the PARs on the surfaces of trophoblast cells shift over the course of the first trimester, suggesting a change in the way the cells interact with proteases during the time when Beard suggested that fetal pancreatic enzymes would influence the behavior of trophoblast cells.<sup>35,75-77</sup>

Beard’s description of a primitive embryonic cell as the origin of cancer is in some ways similar to the modern theory of cancer stem cells.<sup>3</sup> Cancer stem cells are primitive cells included in the tumor mass that possess stem-like qualities, including self-renewal, and if transplanted will

cause tumor development in a new host in experimental models. They are theorized to be responsible for cancer initiation, progression, metastatic spread, and resistance to therapeutic agents. They often display embryonic characteristics, such as markers on the surface of cancer stem cells that are also present on the surfaces of human embryonic stem cells.<sup>78</sup>

In a 2019 article, Hernández-Camarero et al reported that a pancreatic proenzyme combination (chymotrypsinogen and trypsinogen) had anti-tumor efficacy against pancreatic cancer stem cells in vitro and in vivo, including decreases in various cancer stem cell markers and inhibition of engrafting of tumors in nude mice.<sup>48</sup>

## Conclusion

The theory that pancreatic proteolytic enzymes could have an anti-cancer effect is more than a century old. Case reports and small studies with various enzyme preparations have kept the theory alive. One formal clinical trial showed disappointing results, but those results were contested by Gonzalez and Isaacs due to poor adherence and other irregularities in trial administration.<sup>21,22</sup>

Case reports, by their nature, cannot prove that a therapy is effective. But as Vandembroucke<sup>79</sup> states in his article “In Defense of Case Reports and Case Series,” “Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine.” A persuasive theory about a mechanism of action can help the medical research world decide that new ideas deserve attention; a lack of one causes dismissal.<sup>80</sup>

During the 20th century, proteases were thought to have no function beyond digestion. Since then, with the discovery of the broader role of proteases in physiology, the possibility that pancreatic enzymes can have an anti-cancer effect is more intriguing. Promising in vitro and in vivo results and case reports, as reviewed in this paper, support the argument for more research. If pancreatic enzymes and/or proenzymes prove to be effective against cancer stem cells, they would be an extremely valuable addition to the oncologic armamentarium.

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