Integrative Cancer Therapies
Volume 7 Number 4
December 2008 229-251

10.1177/1534735408326174
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The Life and Times of John Beard, DSc (1858-1924)

Ralph W. Moss, PhD

The British developmental biologist John Beard, DSc (1858-1924) is little remembered today. Yet, he made outstanding contributions to the life sciences. Beard deserves to be included among the leading biologists of the late 19th and early 20th century. He has been hailed as a forerunner of the present-day theory of the cancer stem cell (CSC). He was the first to point to the parallels between cancer and the trophoblastic cells that envelop and nourish the embryo, characterizing cancer as "irresponsible trophoblast." He pointed out that the initiation of fetal pancreatic function coincided with a reduction in the invasiveness of trophoblast, which otherwise might progress to clinical cancer (ie, choriocarcinoma). Based on the above propositions, he recommended the therapeutic use of pancreatic enzymes in treating cancer and other diseases. This therapy created a worldwide controversy, and although rejected in his day, persists in the world of complementary and alternative medicine (CAM) today.

Keywords: cancer, Trophoblast, beard, enzymes, Trypsin, pancreas

> In spite of the present condemnation of trypsin, there is still a large chance that time will tell another story.[1]
>
> —*New York Times*, October 9, 1909

> The really new, when it is far-reaching and thorough, can only gradually find an entrance, because numerous convictions must be altered in order to make its proper place for the newcomer.[2]
>
> —John Beard

The British developmental biologist John Beard, DSc (1858-1924) is little remembered today, even by medical historians. Yet he made outstanding contributions to the life sciences.

- He was the first to describe the evolution of the nervous system of elasmobranch fishes. "Into the differences of opinion and confusion in this field of research Beard, in 1884, introduced a semblance of order," wrote Dr. Frederic Lee in 1898.[3]
- He demonstrated the morphological continuity of germ cells in several vertebrate species.[4] "The work was carried out on extensive material, embracing all the chief epochs of development," wrote Dr Agnes Claypole of Cornell University in 1900.[5]
- He codiscovered the large, transient sensory cells of the spinal cord, still known as Rohon-Beard cells.[6-9]
- He was the first to propose that the corpus luteum was responsible for the inhibition of ovulation during pregnancy.[10]
- He was among the first to describe programmed cell death, or apoptosis. Beard described "the programmed loss of an entire population of neurons in fish embryos."[11]
- He was the first to describe the thymus—long believed to be a vestigial organ—as "the parent source" of the lymphoid structures of the body.[12]

Because of this steady stream of discoveries, presented in more than 100 scientific papers and monographs, Beard was honored by the French Academy of Sciences (1890) and nominated for the 1906 Nobel Prize for Medicine. From the vantage point of our century, when apoptosis alone is the subject of 130,000 and more scientific articles, Beard's contributions appear even more substantial than they did to his contemporaries (Jacques Miller, personal communication, Sept. 9, 2007). John Beard deserves to be included among the leading biologists of the late 19th and early 20th century.

That said, it would be unusual to devote an issue of a medical journal to the legacy of an underrated scientist, even in the sesquicentenary of his birth. The main reason for remembering him now is because of what has turned out to be the innovative, one might say prescient, nature of his ideas on the etiology of cancer. Indeed, Beard's thinking on the origin of cancer has been hailed as a

From Cancer Communications, Lemont, Pennsylvania

Address correspondence to: Ralph W. Moss, PhD, Cancer Communications Inc, Box 1076, Lemont, PA 16851; e-mail: ralph@cancerdecisions.com.

forerunner of the present-day theory of cancer stem cells (CSCs). "Cancer arises from displaced trophoblast of activated germinal cells," wrote Stewart Sell, MD, in his *Stem Cell Handbook*.[13] In this book, Beard's name follows that of Virchow, Durante, Cohnheim, and Wilms in anticipating today's CSC theory.

But his hypotheses were even more far-reaching, and included novel ideas concerning the pathogenesis and treatment of cancer. For example:

- He was the first to point to the parallels between cancer and the trophoblastic cells that envelop and nourish the embryo, characterizing cancer as "irresponsible trophoblast."
- He pointed out that the initiation of fetal pancreatic function corresponded temporally with a reduction in the invasiveness of trophoblast, which otherwise might progress to clinical cancer (ie, choriocarcinoma).
- Based on the above propositions, he recommended the therapeutic use of pancreatic enzymes in treating cancer and other diseases.

These interrelated propositions have had an extraordinary afterlife. In the 21st century, the similarity of cancer to trophoblast has become a scientific commonplace. A 2007 review concluded: "Trophoblast research over the past decades has underlined the striking similarities between the proliferative, migratory, and invasive properties of placental cells and those of cancer cells."[14] Most of the molecular byproducts characteristic of trophoblast are shared by cancer, and vice versa. Some embryologists refer to trophoblast as a "pseudomalignancy."[15,16] Beard said as much 100 years ago, although his prior claim on this discovery is not always acknowledged by present-day researchers.

Similarly, over the past 30 years, the therapeutic use of enzymes has become a part of conventional medical practice. In January 1978, the US Food and Drug Administration (FDA) approved the enzyme asparaginase in the treatment of acute lymphocytic leukemia. In the same month, the FDA approved urokinase as a treatment for acute myocardial infarctions and pulmonary embolism.[17] In January 1998 the FDA granted orphan drug status to an oral enzyme combination for the treatment of multiple myeloma (although the trial was never completed).

The FDA has also granted a new drug application (NDA) for the use of pancreatic enzymes in the treatment of the pancreatic exocrine insufficiency, associated with cystic fibrosis and chronic pancreatitis. They are also sometimes used for pancreatic insufficiency associated with pancreatic cancer. (Such preparations are often enteric coated to avoid degradation by stomach acids.) A large pharmaceutical company, Genzyme, is based around the use of various enzyme products for treating rare diseases. For example, Cerezyme® (imiglucerase for injection) is now the standard of care for patients with type I Gaucher disease.[18]

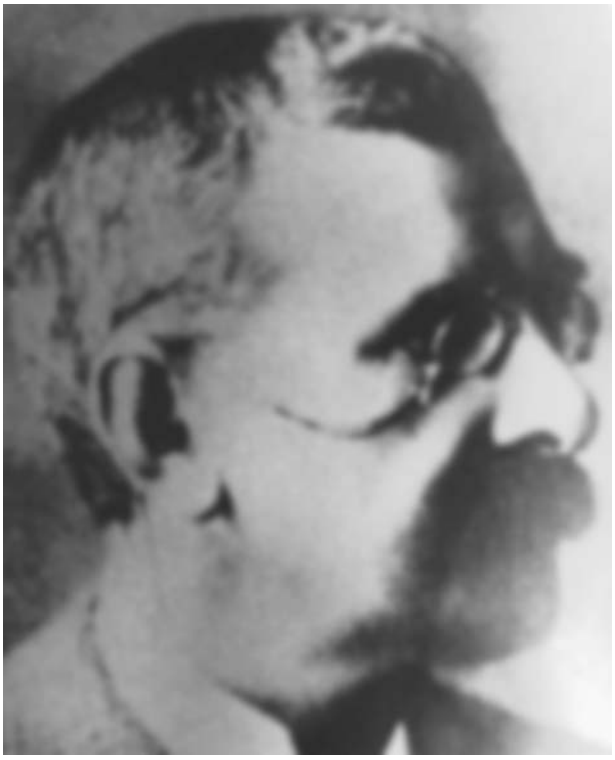

Figure 1. The only known photograph of John Beard.

Enzymes, such as Wobenzym N, are also an increasingly popular over-the-counter treatment for sports injuries, as well as a variety of inflammatory conditions. Indirectly, John Beard was the progenitor of all such developments in the therapeutic use of enzymes.

Origin and Early Education

Who then was John Beard? Until now, few details of his life have been available and published statements about his life, more often than not, have been erroneous. For instance, I have seen him described as John Beer, the Scottish, Welsh, or American physician, born in 1857, died in 1915, 1919, or 1923, who lived alone and left no heirs. As the reader will see, every one of these so-called facts is untrue. The emergence of online research tools, along with more traditional methods of historical inquiry, now enables us to trace the lineaments of a fascinating life and scientific career.

John Beard was born on November 11, 1858, in the parish of Heaton Norris, a southern suburb of industrial Manchester, UK. His grandfather, John, was an unskilled mill operative, but his father (also surnamed John), who had no formal education beyond grade school, rose to become a clerk in a nearby mill. This would have indicated

unusual drive and ability. The family rented a house on Reddish Lane, a neighborhood of white-collar employees of the city's sprawling cotton industry. They were comfortable enough to employ a full-time servant.

Suddenly, in the spring of 1866, Beard's father died at the age of 31 years old and Beard's mother, Eliza, was left with the sole responsibility for 3 sons: John (aged 8 years), Samuel Barlow (aged 6 years) and an infant named David. Although Eliza came from the same lower middle class background as her husband, she was evidently left with some resources. In the 1871 census she is described as a woman "of independent means," although those means were far from ample. The full-time servant was dismissed and the family moved to a nearby neighborhood of blue-collar workers.

In the winter of 1873 the family's fortunes suddenly improved when, at age 36 years old, Eliza married a cotton fabric manufacturer named William Halliwell (1831-1884). The family then moved to Littleborough, Rochdale, 18 miles north of their former home in Reddish. In October 1873, Halliwell sent John and his younger brother Samuel to King's School, Grantham. Founded in Lincolnshire in 1329, King's School was best known for its most famous alumnus, Sir Isaac Newton. John Beard attended King's School for nearly 2 years, until midsummer 1875, when he left before graduating. His reasons for leaving are unknown, but were unlikely to have been financial in nature, since his brother Samuel stayed on, and David later attended King's School as well. One possible explanation for John Beard's leaving King's School was his growing interest in science. The courses at King's School primarily consisted of Greek, Latin, and Hebrew, plus a little mathematics, but with no scientific or modern language instruction (Yvette Gunther, personal communication, Sept. 28, 2007).

Beard finished his secondary education near home and in 1877 registered at Owens College, Manchester. Owens was a relatively new institution funded through the bequest of a wealthy cotton merchant, John Owens. (Owens is now incorporated into the University of Manchester.) It was the first of the civic or "redbrick" universities in Great Britain. One important innovation was the absence of a religious test, such as adherence to the 39 articles of the Anglican faith for students or faculty. This was in contradistinction to many other British educational institutions, in which a religious pledge was required before some degrees could be conferred. It also emphasized the study of practical sciences over more theoretical subjects or the classics.

Owens was particularly strong in the newly emerging evolutionary biology and Beard studied with Arthur Milnes Marshall (1852-1893) a young professor of zoology there. In his later writings, Beard warmly thanked Marshall as both friend and mentor. On several occasions he returned to Owens and eventually received both an earned baccalaureate (BSc) and an honorary doctorate (DSc) from the college. Nonetheless, on this first occasion he did not take a degree but matriculated at the University of London. He completed his baccalaureate exams in the natural sciences from the University of London in 1878, according to an application he submitted to the University of Freiburg (Frederick B. Churchill, personal communication, July 23, 2007.)

In the winter of 1878, Beard's family suffered a second blow when his mother, Eliza, died in Rochdale at the age of 40 years old. A few years later, in the winter of 1884, his stepfather, William Halliwell also died, at the age of 53 years old. Beard's birth family then effectively dispersed. His brother, Samuel, married, had children, and became a commission agent for Manchester goods. His brother David was also employed in the cotton business, but never married, lived in a succession of boarding houses, and died in Manchester in 1910 at age 44 years old.

I believe that in the period 1878 to 1880 Beard enrolled in medical school. In a later article, he volunteered that in the year 1879 "I often saw Professor Edward Lund and Mr Sam Bradley perform major operations under Listerian methods as they then were."[19] Edward Lund, FRCS (1823-1898) was a professor of surgery at Owens College of Manchester University and a consulting surgeon at the Manchester Royal Infirmary. Since Beard says he witnessed many operations in this time, the most likely explanation is that he was a medical student during this period, but decided not to pursue medicine and to go into scientific research. Perhaps, like Charles Darwin, he didn't have the stomach for the brutal operations of the day.

In the academic year 1880 to 1881, Beard attended the Royal School of Mines (RSM), South Kensington, London. (The building is now a wing of the Victoria and Albert Museum.) His reason for attending was to apprentice himself to Professor Thomas Henry Huxley (1825-1895), who, after his mentor Darwin, was the most famous English scientist of the day and a man of enormous energy and accomplishments. Later, Beard would regale students with anecdotes about his famous British mentor and sometimes also emulate Huxley's acerbic style of argumentation.

Graduate Study in Germany

In the summer term of 1881, Beard returned to Owens College where he studied chemistry with Sir Henry Enfield Roscoe (1833-1915), discoverer of the chemical element vanadium. But his eyes were increasingly turned toward Germany, which then held undisputed leadership in biology. To be scientifically well educated one had to read German, as Huxley did, and preferably to study at a German university, as Roscoe had done. Perhaps at Roscoe's urging, Beard decided to earn his doctorate in biology with these world experts. He later proudly boasted

of "those who made me, the scientific Germans." (Frederick B. Churchill, PhD, personal communications, July 23, 2007)

In the fall of 1881, he matriculated at the Albert Ludwigs University of Freiburg in Breisgau, in southwest Germany, a venerable institution that was founded in 1457. His intention was to study with Friedrich Leopold August Weismann (1834-1914), director of Freiburg's Anatomical Institute. The 20th century biologist and historian of science, Ernst Mayr of Harvard, has ranked August Weismann as the second most influential evolutionary theorist of the 19th century, after Darwin himself.[21] The path to scientific success, then and now, often began by affiliating oneself with an eminent mentor. Beard would soon claim two, T. H. Huxley and August Weismann. Years later, Beard revered the memory of Weismann, calling him a "good and faithful servant of mankind."[22]

Although formally enrolled at Freiburg, Beard moved within the German university system. This was not uncommon; for example, the zoologist Anton Dohrn (1840-1909) changed universities five times as an undergraduate.[23] Beard soon narrowed his dissertation topic to the study of the evolutionary development of the sensory organs of fish and went where the opportunities for study seemed most promising. From the fall of 1882 until the summer of 1883 he attended the University of Würzburg, working under Professor Karl Semper, a leading figure in biology, whom the *New York Times* called "fully abreast of the times" (April 17, 1881). Beard later thanked him for his "untiring advice and assistance." But in other ways this was a poor choice, as Würzburg is 400 miles from the nearest large body of water, the North Sea. Beard later candidly referred to his year in Würzburg as "very barren, being made in what appeared to be a dreary and empty field."[24]

In September 1883, Beard returned to Freiburg to matriculate for his second year, but then immediately went to Italy, where he spent the half of the year from November 1883 to April 1884 studying and working at the Stazione Zoologica in Naples. Despite its Italian name and location, the zoological station was a continental institution, whose proceedings were published in German. Under a unique arrangement, various European states maintained their own "table" (ie, work area) at the station, which in return provided research facilities for promising scholarship students. The Senate of the University of Freiburg, at Professor Weismann's urging, had nominated Beard for this position, but the Bavarian government then failed to fulfill its financial commitment.

This was a time of great financial and political turmoil in Bavaria, which culminated in the deposition and death of King Ludwig II in 1886. Thus, Beard traveled to Naples uncertain of the terms of his tenure. He later thanked the station's founding director, the aforementioned Anton Dohrn, for providing him with a place at the Bavarian table (presumably at no cost to himself). "For this and many other acts of kindness I beg to tender him my best thanks," he wrote. Founded in 1873, the Stazione remains the oldest aquarium in continental Europe and now bears Dohrn's name. Dohrn founded and maintained the Stazione with his own funds (he was heir to a sugar fortune), along with income generated by visitors to the aquarium.

In April 1884, Beard returned to Freiburg to complete his dissertation, using the microscope slides and knowledge he had obtained in Naples. His major subject (Hauptfach) was zoology, while his minors (Nebenfächen) were physics and botany. Three months later he received his doctorate from the philosophical faculty. His dissertation, submitted in English, was "On the Life-History and Development of the Genus Myzostoma (F. S. Leuckart)." (Myzostomes are small parasites of echinoderms, primarily crinoids, which remove food from grooves in the skin of their hosts.) Wilhelm Engelmann, a scientific publisher in Leipzig, released Beard's first work later that year. It was virtually identical to a long article that he had already published in the zoological station's scientific journal.[25] (Only 3 copies of this work are found in the world's libraries. I own a 4th, which Beard inscribed to Professor A. Macalister, MD, of the University of Cambridge, "with the author's comp[liments]." This is among the very few samples of Beard's handwriting, much less possessions, known to exist.)

Sometime during his stay in Germany, Beard married Henriette Marie Sester (1860-1894), the daughter of a Bavarian farmer named Josef Sester, and his wife, Marie LeFevre Sester. Henriette and Marie LeFevre are of course French names and since Freiburg is only 14 miles from the French border, it is a likely that Henriette's mother, Marie LeFevre, was of French origin. According to British law, on marrying Beard, Henriette became a naturalized British citizen, and could thus follow her husband to the United Kingdom as well.

Return to the United Kingdom

In the summer of 1884, the young couple returned to Manchester where John took up a postdoctoral position as Bishop Berkeley Fellow of Owens College. Because of the courses he had already taken there, he earned a bachelor of science degree from Manchester in the following year. In the following September (1885) Beard's only child, Carl Edgar L. S. Royle Beard (later known as Edgar R. Beard), was born in Chorlton, Lancashire. At the time, Beard was 27 years old and Henriette was 25 years old.

Beard's major scientific interest at that time was the evolutionary development of sensory organs in various fish, especially the genus elasmobranch (sharks, rays, and skates) and ganoid (sturgeon, gar, etc). In 1885 to 1886, he completed a line of research on these fish that he had begun in

Würzburg. He warmly thanked Professor Marshall for the use of his library of zoological works as well as his "valuable assistance, criticism, and advice."[24] In the academic year 1886 to1887 Beard received a grant of £150 from the Royal Society of London for further elasmobranch and ganoid research.[26] Having finished his postdoctoral fellowship at Owens, from July 1887 through the spring of 1889, Beard returned to Germany, where he served as the personal research assistant to Professor Weismann.

Between April and June 1889, Beard made a visit to Black Lake in upper New York State, a remote location that is still described as "nature's fish hatchery." The purpose of this visit was to continue his study of the development of ganoid fish. In particular, he was seeking samples of *Lepidosteus osseus*, or the American bill fish, also called the long-nose garpike. In 1878, the celebrated Harvard anatomist, Alexander Agassiz (1835-1910), had reported the recovery of eggs and embryos of Lepidosteus from this lake near the St Lawrence River. Black Lake, said Beard, was the "well known habitat [of] multitudes of *Lepidosteus*. . . . I sought and found more material than I wanted."[26] Garpike still abound in the lake. In this remote, self-named "fisherman's paradise," Beard probably stayed at the one rustic hotel, which burned down in the early 20th century.

Beard left Black Lake on June 22, 1888, with what he called an "extensive assortment of preserved material of fish development." It was while studying this material, collected in this remote American setting, that Beard made a memorable discovery, one that ultimately led to his later theory of cancer. By painstakingly examining microscope slides of various early stages of *Lepidosteus,* Beard discovered sensory neurons located within the dorsal zone of the spinal cord, which were assembled and subsequently disassembled in the course of the fish's early development. This transient nervous system persisted until it was replaced by the development of the dorsal root ganglia. In effect, *Lepidosteus* went to the trouble—for unknown reasons—of producing two nervous systems in consecutive order, the first of which group outside the normal embryonic development of the latter. It was a most curious finding.

"According to tradition," Beard wrote, "the development of the vertebrate nervous system has hitherto seemed to proceed straight on in a gradually ascending path, without turnings, temporary expedients, or regressive changes. As a consequence, none were looked for and none were found."[27] Beard's thinking proved flexible enough to notice and describe this regressive element in evolution.

Beard described this discovery and, on returning to England, Professor Huxley forwarded it to the Royal Society for publication. Unbeknownst to them, however, others had already seen and described similar cells in other vertebrates. Francis Maitland Balfour (1851-1882), a young naturalist who fell to his death in the Alps, first described them in 1878.[28] Five years before Beard, Josef Victor Rohon (1845-1923) of Prague, described a similar

Figure 2. Lepidosteus osseus (now more commonly called Lepisosteus osseus)

type of cell in the trout, although his discovery was published in an obscure German publication and was little remarked at the time.[29]

Beard then independently rediscovered them in *Lepidosteus* and described them in greater detail. In 1911, they were named Rohon-Beard cells, in honor of the two major co-discoverers.[30,31] As stated above, the behavior of Rohon-Beard cells has recently been described as one of the first known descriptions of programmed cell death, or apoptosis, a concept of enormous importance in modern biology.[11] Beard is now therefore recognized as co-originator of one of the most important ideas in the life sciences.

For Beard, however, the transient appearance and disappearance of these cells triggered a complicated and lengthy chain of reasoning that went beyond the debates of the time. It became, for him, a question of how vertebrate life actually developed and led him to the controversial thesis that what he and others were observing was actually the "alternation of generations" in vertebrates. "The finding of a few stray ganglion cells in the development of an American bill fish (*Lepidosteus osseus*)," he later wrote, "led ultimately to certain thoughts on sexual and asexual generation in animals."[32]

Linnaeus first named this olive brown fish in 1758. It ranges between 24 and 40 inches and when mature it weighs between 1 and 7 pounds. Its body is cylindrical and covered with diamond-shaped scales. Its snout is twice the length of the rest of its head and it has a narrow peak that contains many large teeth. These fish, which are voracious predators, mainly inhabit backwaters near vegetation and twilight is considered the best time of day to fish for them. Although the flesh is edible, the roe is poisonous, and thus it is not a popular food fish.

"The two nervous systems crop up again and again in my published writings since 1888," Beard wrote in his 1911 book. "All my original work, from 1888 down to today, is impregnated with facts concerning the two nervous systems, and the antithesis underlying them. . . ."[20]

In brief, Beard became convinced that there was an "antithetical alternation of generations" in vertebrates,

even humans. Botanists routinely saw and discussed such a fluctuation between haploid and diploid forms in plants.[33] There was also an alternation of generations in some jellyfish (eg, the *Discomedusae*).[34] However, few scientists, then or now, were willing to follow Beard in ascribing the same course of development to vertebrate animals. In his time, only his colleague J. A. Murray accepted and adopted this position. In the 1950s Charles Gurchot, PhD, attempted to update Beard's theory of alternating generations among mammals.[35] However, given the importance of the alternation of generation in plants and some lower animals, it is surprising that Beard's proposition never received more serious consideration.

Edinburgh Years

With his Freiburg doctorate and his paper on *Lepidosteus* in the *Proceedings of the Royal Society of London,* Beard was positioned to begin a successful research and teaching career in the United Kingdom. In August 1889, he was appointed naturalist in charge of the Marine Laboratory at Dunbar, a research center on the coast of Scotland maintained by the Scottish Fishery Board. The Dunbar Station employed 3 young people, of whom the 30-year-old Beard was senior member. This modest post proved to be a stepping-stone to a better position at the nearby University of Edinburgh.

In 1890 Beard was appointed the senior assistant to James Cossar Ewart, MD (1851-1933), Regius professor of natural history, in the Department of Natural History. Beard remained Ewart's deputy for the next 20 years. In 1894, on the untimely death of George Brook (1857-1894), a fellow Owens graduate, Beard was also appointed lecturer in comparative embryology and anatomy of vertebrates. Later in his career he added lecturer in cytology to his job description.

The initial salary for a university lecturer in Great Britain at that time was around £250. On retirement, this would have risen to about £500, a decent sum (about half the price of a new house, according to the *New York Times*, June 4, 1922), but nothing like the salary of a full professor or a successful medical doctor. Since he had few grants, most of Beard's research was carried out at his own expense.

"The funds for research are not ample," he once explained in the *Lancet*. "From 1890 to 1898 these researches were carried out from my own slender private means and without grants from any source. Every bit of my published work has left me poorer than when the research was commenced."[36] For more than 30 years he and his small family led a lower middle-class existence in a succession of apartments and houses in and around Edinburgh. There is no sign of any extravagances. Every extra pound seems to have gone for his privately funded research, plus occasional return visits to Germany.

The University of Edinburgh was a world-famous medical institution, considered in the United Kingdom to be second only to Oxford, and Beard had attained a good position. But given his first-rate education, burgeoning list of publications, and outstanding mentors, it is surprising that he never progressed further in his academic career. The next steps up the ladder would have been a fellowship in the Royal Society and then a full professorship, ie, chairmanship of his own department.

The main problem was that Professor Ewart was firmly ensconced in his position, and although 7 years older than Beard, outlived him by almost a decade. In the European system, there was only a single professor, the chairman, and consequently no room for Beard or anyone else to advance much further until the professor retired or died. Not only did the University of Edinburgh have no professorships specifically in Beard's field, but, as Beard himself tells us, there was not a single full professor of embryology in all of Great Britain.[37,38] In contrast, in Freiburg, Beard wrote in his 1911 book, embryology was a required subject for all medical students. On a return visit to his alma mater in 1910 he found his former colleagues' lecture halls crowded with students, so much so that the professors did not know where to put them all. Meanwhile, at the University of Edinburgh, embryology was a poorly attended elective.

In the first years of the 20th century, there was a campaign to create a chair in embryology for Beard at the University of London, but this ended abruptly when his main champion, Professor George Bend Howes (1853-1905), died unexpectedly at 52 years old.[39] Edinburgh did not create an autonomous Department of Zoology until 1919. By then Beard, the logical candidate for professor, was already ill and was passed over in favor of a younger colleague, James Hartley Ashworth.

Beard's career might have progressed more smoothly had he attained control of his own department. Contemporary accounts paint a generally unpleasant picture of life in Edinburgh's anatomy department. We hear of "cramped quarters" and a "depressing atmosphere."[37] The young scientist, James Peter Hill, called it a "stagnation place." Beard had a small office in Old College, but was forced to do most of his scientific work during spare hours at home, working with his Zeiss microscope and slides on the dining room table.[40]

What sort of teacher was Beard? According to *Nature,* in his prime Beard was "a stimulating teacher, one who aroused the true spirit of investigation in his pupils."[41] Several scientists have left records crediting him with inspiring them to enter the field of biological research. Not everyone agreed, however. In a World War II-era memoir of his Edinburgh education, Sir John S. Flett, FRS, called Beard "somewhat of a crank. . . and anything but a good teacher." This is how this one alumnus

recollected his student days. Of course, Flett's field was geology, not biology, but Beard seemed to have a diminishing interest in training young people to become doctors. "Ten years ago," he wrote in 1915, "I used to say that I had no desire to teach embryology to any pathologist, but now I have come to feel the futility of trying to teach embryology to the medical profession in general."[42]

What mattered most to Beard was clearly his own research. This detailed work, which included patiently counting, recording, and illustrating the migration of germ cells, required an extraordinary degree of concentration. Peace and quiet could not have been easy to attain in a small rented flat with a wife and child, on a crowded and treeless urban avenue. Then, on November 4, 1894, his problems were compounded when tragedy struck: Henriette died at their home at 55 Comely Bank Road, at just 34 years old. The cause of death was acute pneumonia. It is worth noting that Edinburgh, at this time, was nicknamed "Auld Reekie," ie, Old Stinky, because of its severe air pollution problem.

Despite personal difficulties, for 2 decades, from 1885 to 1905, Beard remained exceptionally productive. In addition to a stream of approximately 100 scientific articles, he published 5 monographs: *Morphological Studies* (London, 1888), *On Certain Problems of Vertebrate Embryology* (Jena, 1896), *The History of a Transient Nervous Apparatus in Certain Ichthyopsida* (Jena, 1896), *The Span of Gestation and the Cause of Birth* (Jena 1897), and *The Determination of Sex in the Animal Kingdom* (Jena, 1902). On the whole, these were well received in scientific publications. *The Span of Gestation* in particular was discussed around the world. One even finds a discussion of it in the correspondence of Sigmund Freud and his closest friend and confidant, Wilhelm Fliess, MD, who drew on it as support for a controversial theory called "vital periodicity."[43]

Beard remained conversant with German scientific literature throughout his life, and in fact many of his own articles first appeared (albeit in English) in German journals—especially the *Anatomischer Anzeiger*, to which he was a steady contributor. His writings also appeared in the leading British journals, *Nature, Science*, the *British Medical Journal,* and the *Lancet*. He wrote on such diverse topics as the origin of the cranial ganglia (1885), sensory organs (1885), parietal eye (1887) and teeth in fishes (1888), the determination of sex (1902), etc. He also produced original work on the following species: *Myzostoma glabrum* (1884, 1888, or 1898), *Ichthyopsida* (1890), sharks (1887), *myxonoid* (1888), *cyclostome* (1888) and *marsipobranch* fishes (1889), *Lepidosteus osseus* (1889), *infusoria* (1895), lampreys and hags (1892), *Scyllium* (1896), *Tricosurus vulpecula* (1897), and a special topic of interest, *Raja batis*, the common or smooth skate (1896, 1900, 1904). (See "Timeline of the Life of John Beard (1858-1924)," pp 252-261.)

A writer for *Nature* later said, "Beard had a keen mind and was a forceful writer. He had great skill in zoological technique and he formed a large collection of microscopical preparations—chiefly complete series of sections—for the study of the development of *Raja*."[41] The basis for his remarkable productivity was this private collection of thousands of microscope slides showing the various stages of anatomical development, mostly of *Raja batis* and other fish embryos, which he prepared, first in Germany, and then in Naples, New York's Black Lake, and along the northeast coast of Scotland. With them, he could follow the progression of whatever organ or morphological change he was interested in. This was how he eventually established the role of the corpus luteum in menstruation and described the thymus as a "parent source" of the lymphoid tissue and how he hit on his cancer theory.

Before the turn of the century Beard began to be increasingly concerned with the nature and fate of germ cells. With only the help of an amateur microscopist who took an interest in his work, Beard patiently traced the development and migration—the "morphological continuity"—of the germ cells in *Raja batis* (1900). A high point came when the great Johns Hopkins physician, Sir William Osler, lauded this work in his celebrated lecture, "Science and Immortality."[44]

Growing Interest in Human Biology

John Beard was increasingly concerned with the relationship of his findings in fish to mammalian and even human development. In 1897, he first ventured into an area with a direct impact on human medicine. He published his pioneering paper on the role of the corpus luteum. He noted the coincidence of the corpus luteum with gestation and suggested, on purely theoretical grounds, that it was essentially an organ of pregnancy, ie, that it served a necessary function during the course of gestation, probably in the maintenance of conditions essential to pregnancy. "His reasoning was strictly of the armchair variety," wrote one scholar, "but it is striking to reflect how closely he hit upon the truth."[45]

Auguste Prenant (1861-1927) confirmed Beard's finding in the following year and, soon afterward, the Philadelphia pathologist Leo Loeb experimentally confirmed his thesis by removing the corpus luteum in guinea pigs and accelerating their ovulation.[46] Despite the truth of Beard's assertions on the corpus luteum, Harvard Professor Charles S. Minot (1852-1914) attacked him in the pages of *Science*. "The tendency to push speculation indefinitely beyond observation. . . has been marked previously in Mr Beard's previous papers. . . ."[47] Minot claimed. In this instance, however, Beard's scientific instincts about the corpus luteum proved correct.

In 1897, Beard wrote about the rhythm of reproduction in mammals. His findings on the thymus and the immune system, as well as the corpus luteum, were of immediate interest to students of medicine. His conclusions on the fate of germ cells in elasmobranch fish led eventually to his conclusions on cancer in mammals, including humans. As the Michigan pathologist Alfred Scott Warthin wrote in 1902, "To any but vertebrate embryologists there might appear to be no warrant for applying results obtained in animals so low down in the scale to man himself."[48]

The broad outlines, the laws, and even many of the details of embryogenesis are in fact common to both man and fishes. Since Beard had observed that between 10% to 12% of germ cells go astray in the formation of *Pristiurus* and between 25% to 30% in *Raja batis*, it was logical for him to assume that a similar process was at work in humans. In animals these vagrant germ cells seemed to settle precisely in those folds, holes, and corners of the body where cancers in humans were also most common.

Sometime between 1894 and 1901, Beard remarried. His second wife, Helen, was the daughter of a Prussian military official, Col Eduard von Roschmann. She was born on June 26, 1864, and thus was over 30 years old when Beard married her. Circumstantial evidence suggests that the marriage took place in Germany in 1897, a year in which Beard was away from Edinburgh on a sabbatical and may have visited his Freiburg alma mater (as he did on a subsequent sabbatical in 1910). (Helen's census records state that she was a "British subject by message, Wittenburgh." I believe this is a British clerk's misspelling of "Württemberg," a former state in the southwest of Germany. According to immigration records, four men named Roschmann emigrated from Württemberg between 1840 and 1858. There is no record of Helen and John getting married in the United Kingdom but she certainly could have become a British subject by marrying Beard in Württemberg, a fact that would then have been confirmed by a telegram from the British consulate.)

Like other British biologists, Beard may have gone to Germany that fall for the *Verein für Naturforschung* meeting in Brunschweig (Brunswick). The central topic was the placenta and the chairman was the legendary Ambrosius Arnold Willem Hubrecht (1853-1915), who, in 1889, had first discovered the trophoblast in the European hedgehog. In any case, we know that Helen soon joined him and his son Edgar (aged 12 years) in their Edinburgh home.

Development of the Cancer Theory

We now come to the work for which John Beard is best remembered—his enzyme treatment of cancer.

Some have suggested that indigenous populations used papaya-based enzymes to treat cancer.[49] But Beard was no follower of folk medicine. His proposal for the use of pancreatic enzymes against cancer was neither the result of an interest in folk medicine nor was it serendipitous. He suggested the therapeutic utility of such enzymes as the final step in a lengthy exploration of embryonic development, particularly of germ cells. His teacher, August Weismann, had originated the germ plasm theory of heredity.[50] Starting in the 1880s, Beard himself expanded this concept through his research on germ cells in specific vertebrate species, particularly elasmobranch fishes.

By 1902, Beard had concluded that cancer arose as the result of the presence and transformation of aberrant germ cells that had lost their way in their journey to the gonads in the course of embryogenesis. The activation of these primordial germ cells resulted in the formation of what Beard called "irresponsible trophoblast." Cancer was thus a normal cell (one routinely generated in the course of mammalian pregnancy) that had been stimulated to multiply at the wrong time and place. That is why Beard spoke of cancer as a natural phenomenon that was known as a malignant disease. In doing so, he contradicted hundreds of years of medical thinking, which routinely depicted cancer as an abnormal growth *contra naturam*, ie, contrary to nature.[51]

Beard believed that the trophoblast represented the larval or asexual phase of human development. For technical reasons, Beard invented the term *phorozoon* to more accurately represent this entity. He also noted that embryo and trophoblast existed in a kind of tension that was mutually dependent but also antagonistic. At the triumphant moment of birth the placenta finally dies and is ejected as the afterbirth. He later came to believe that the nature of the proteins in cancer and in normal tissue were stereotactically different. To Beard, at least, his theory of cancer, and ultimately his proposal for treating the disease, flowed smoothly from his prior scientific work, starting with his 5-month sojourn in upstate New York in 1889.

Beard's proposal of cancer as trophoblast met with a furious reaction from one prominent British scientist. W. Roger Williams, FRCS, was a London surgeon and prolific author in the field of cancer. In December 1904 he wrote to the *Lancet* to complain that Beard had appropriated his key ideas about cancer and trophoblast without crediting him.[52] It was virtually a charge of plagiarism. What initially gave the charge some credibility was that in July 1902 Williams had sent Beard a copy of his 1888 book on cancer, in which he put forward somewhat similar ideas.[53] Beard had failed to acknowledge the gift.

However, Williams' ideas were vaguely about growth, where Beard's were highly focused on the trophoblast. Williams wrote that cancer and normal growth were "protean manifestations of one common process, which underlies and is the cause of them all—to wit, cell growth and proliferation. . . under favorable conditions, certain

cells may take on independent action, growing, and multiplying, without regard to the requirements of adjacent tissues, and of the organism as a whole."[54]

In a long rebuttal letter, published in the *Lancet* in January 1905, Beard made a convincing case that his own ideas were sufficiently different than those of Williams to rule out any idea of plagiarism.[55] Nevertheless, it was one in a string of embarrassments that raised questions about Beard's integrity. Beard subsequently thought (based on stylistic considerations) that Williams was behind some anonymous attacks that he later endured in the British medical press.

In November 1904, Beard had hypothesized that the initiation of pancreatic enzyme production by the fetus might be responsible for the regression of trophoblastic tissue in the natural course of pregnancy. Given the perceived similarities in cellular morphology and behavior of trophoblast and cancer, Beard postulated that pancreatic enzymes of mammalian origin should be tested in cancer patients. He confidently predicted that enzymes would prove to be an effective treatment and indeed the natural cure for cancer. As we shall see, starting in 1905, some doctors responded to this suggestion. With a medical colleague, Beard was personally involved in planning the treatment of several patients, including at least one who, it was claimed, had a complete remission as a result of this treatment.

At the inception of the cancer controversy, Beard was considered among the leading embryologists in the world. In an 1898 review, the *Lancet* had summed up his professional standing: "The views advanced by Dr Beard appear to us to be original and to be well worthy of the attention of all those who are interested in embryology."[56] In 1906, the *New York Times* editorialized: "With the possible exception of Weismann of Freiburg," ie, his own teacher, Beard was "the foremost living student of germinal or embryonic tissue. His utterances in regard to matters within his scientific domain are authoritative and universally regarded as final" (December 23, 1906).[57] Even those who opposed his ideas about cancer admitted that he "brought to the work a scientific spirit, a mind trained in the verification of hypotheses in his own work, and a reputation for earnestness and sincerity of purpose which at once inspired confidence."[58] If embryology had anything to contribute to the search for a cancer cure (and today that is regarded as self-evident[59]), Beard was certainly qualified to make this contribution.[60]

Because of Beard's outstanding reputation, and an emerging cohort of supporters around the world, his activities, in a sense, precipitated the first international controversy over an alternative treatment for cancer. (In doing so, it may have provided the template for many subsequent controversies.) Between 1905 and 1909, his ideas were debated in leading magazines and newspapers, and even on the floor of the House of Commons. In the United Kingdom, United States, Germany, Switzerland, and Italy, reports were published in peer-reviewed journals, including 3 in the *Journal of the American Medical Association*, supporting his therapeutic concepts. A survey conducted among physicians in New York State in 1907 showed that 1 out of 6 respondents were already using enzymes as a treatment of cancer.[61] During this time, the *New York Times* devoted no less than 38 articles, editorials, and letters to Beard's theories, most of them favorable. Word of his discovery reached as far as China.

Development of the Cancer Controversy

In 1905, Beard stood at the pinnacle of his career. At 47 years old, he had an important teaching job at a prestigious university that, while not very well compensated, gave him the time to pursue research and make his contribution to 20th century scholarship. Although Beard demonstrated little in the way of worldly ambition, membership in the Royal Society, a full professorship, and possibly even a Nobel Prize were not beyond imagining. Yet he had little idea that his seemingly innocuous foray into cancer research would cause a worldwide controversy and damage his scientific reputation.

On June 21, 1902, the *Lancet*, the most celebrated medical weekly in the English-speaking world, published his first article on cancer, "Embryological Aspects and Etiology of Carcinoma." Although his thesis that cancer resembled trophoblast was certainly a bold one, the article itself made little impact at the time. I can find but a single mention of it in the contemporaneous literature. There, a perceptive reviewer remarked, "His paper seems to have attracted singularly little attention and practically no criticism. Medical men. . . who did read the paper did not quite understand it."[62]

Between 1902 and 1905, Beard's thinking about cancer raced forward. On February 16, 1903, he gave a lecture titled "The Embryology of Tumors" to the Eighth Ordinary Meeting of the Royal Society of Edinburgh. His prior public lectures had mainly been to the local botany society, but here was a chance to reach leading scientists with his new theory. Yet, despite the fact that the president of the Royal Society that year was his own department chairman, J. Cossar Ewart, who also submitted the paper, the editors of the *Proceedings of the Royal Society* rejected it for publication.

This was a stunning rebuff to Beard and a turning point in his career. Beard was a proud, even vain man, and for 20 years leading scientific publications in both Germany and the United Kingdom had welcomed his submissions. His half dozen monographs had also been reviewed favorably and given serious consideration around the world. However, cancer was treacherous terrain. Beard explained that critics inside and outside the Royal Society

objected to any pronouncements on cancer by a "mere scientific man, and not even a medical practitioner." To them, he was an owlish biology professor claiming knowledge of matters best left to physicians. To him, their objections were a repeat of Pasteur's legendary rejection by French physicians for being a "mere chemist."

Beard then exacerbated the conflict by sending his lecture to a German colleague, Professor Ernst Heinrich Ziegler (1849-1905), for publication in the *Centralblatt für Allgemeine Pathologie*. Although this was mainly a time of international scientific cooperation, the run up to World War I also witnessed sharp scientific rivalries between the Germans and the Anglo-Saxons. Ziegler pointedly translated Beard's paper into German, so as to reach the widest possible audience of Central European scientists and clinicians. Given Beard's well-known Teutonic connections, this may have appeared slightly disloyal. Publication in Germany must have seemed to him as an effective end run around his critics in the Royal Society, but it also quickly negated any chance of membership in that august society. And a fellowship in the Royal Society, which conveyed the right to put FRS after one's name, was virtually a precondition to high academic advancement.

Then, late in the afternoon of December 8, 1904, while crossing the quad at Edinburgh University, Beard had a kind of epiphany. He suddenly realized that the growth of the trophoblastic cells of pregnancy were halted by what he called the "commencing functional activities of the pancreas gland." The logical corollary of this was that cancer, trophoblastic in its fundamental nature, might similarly be restrained and ultimately destroyed by the therapeutic application of pancreatic enzymes. In other words, he had (in his own mind at least) discovered a potential cure for cancer

Beard specified that the human pancreas began its production of trypsin during what he called the "critical period," which he defined as the period in which organ formation is essentially completed. In humans, he identified this as occurring in the 8th week of gestation. This insight about the early commencement of enzyme production seemed unlikely at the time, since the fetus does not have any need of pancreatic enzymes for digestion until birth. But it was on a par with his other "arm chair" insights into the functional role of the thymus and corpus luteum.

In fact, it is supported by one modern textbook on development: "After the main period of outgrowth, the pancreatic acinar cells pass through another transition before attaining a third, differentiated state," this textbook states. "By this time, they have acquired an elaborate protein synthesizing apparatus, and the inactive forms of the polypeptide digestive enzymes are stored in the cytoplasm as zymogen granules."[63] A graph in that book then shows that enzyme synthesis correlates, on a week-by-week basis, with the development of acinar cells. Synthesis begins to increase exponentially after the seventh or eight weeks, ie, just around the time that Beard predicted.[63] Similarly, Fukayama has found pancreatic secretory trypsin inhibitor (PSTI) in developing buds of the human pancreas during the 8th gestational week.[64]

Although lacking modern methods such as immunohistochemistry, Beard was correct in stating that the human fetus begins production of these enzymes long before there is any need of them for alimentary digestion. Beard was even able to accurately demarcate the initiation of pancreatic enzyme production, possibly to the exact week. Whether he was also right in his belief that this embryonic production was related to antitrophoblastic activity is not as certain. In any case, it was a remarkable theory and was worthy of close scientific study. Instead, it briefly became the focus of a fierce international controversy and the object of scorn and derision from the British medical establishment.

Edinburgh and Liverpool Lectures

On Tuesday, December 13, 1904, Beard gave a lecture titled "Germ Cells in Relation to Malignant Disease" to the Edinburgh Pathological Club (EPC). The EPC, founded in 1886, was a 25-member group, which met monthly to read and discuss short papers on medical subjects, including, but not limited to, pathology. It was here that Beard unequivocally stated his view that pancreatic enzymes might be effective in the treatment of cancer.

A few weeks later, on January 20, 1905, he gave essentially the same lecture to the Liverpool Anatomical Society. Here he repeated his belief that cancer was an "irresponsible trophoblast" and might therefore be controlled by enzyme injections. The EPC version of the speech appears to be lost, but the Liverpool lecture was published in full the next day in that city's *Daily Post and Mercury* (January 21, 1905). I have read a précis of it in *The Scotsman* of Edinburgh, which quotes Beard as saying: "Clearly, then, since cancer was an irresponsible trophoblast, the ferment which brought about the degeneration of this in normal development ought to possess potency when directed against cells of a malignant tumor."[65]

Here was a clear allusion to pancreatic enzymes. The precise dates of these lectures would turn out to have significance for Beard's reputation. By one of those quirks of fate, such as those that bedeviled the careers of Newton, Darwin, and many others, at nearly the same moment another scientist, the London gynecologist John Alexander Shaw-Mackenzie, MD (1858-1931), also suggested using injections of the enzyme trypsin in the treatment of cancer. Let us therefore examine their competing claims to priority.

Shaw-Mackenzie was born in Belgaum, India, in 1858. He was the son of a district session's judge and grandson of a Scottish civil service commissioner. He returned to

England as a youth, received his medical degree from the University of London and became a member in good standing of the Royal College of Surgeons and the British Gynecological Society. Shaw-Mackenzie was a hospital pathologist and also had a thriving private practice at 31 Grosvenor Square (now part of the site of the American Embassy).

Beard did not contest that Shaw-Mackenzie was the first person to actually use trypsin for the treatment of cancer. The latter gave the first injection of trypsin to a patient on January 19, 1905.[66] However, was he also the first person to conceive of the idea? Shaw-Mackenzie had a strong claim. He had published two journal articles advocating the use of pancreatic enzyme injections, which indisputably appeared in print weeks before John Beard's first article on the topic. Thus, Shaw-Mackenzie's first such article was in the *British Medical Journal* on January 7, 1905, followed by a similar one in the *Lancet* on January 14, 1905. In 1905, Shaw-Mackenzie also published a small book on cancer that contained, *inter alia*, recommendations on the use of trypsin injections in cancer. It went through four printings.

By contrast, Beard's first article advocating the use of trypsin in cancer did not appear in the *Lancet* until 3 weeks after Shaw-Mackenzie's, on February 4, 1905. So, if one were to judge solely by which author's work appeared first in print, on these grounds Shaw-Mackenzie would have to be deemed the originator of the enzyme therapy concept.

Beard's claim to priority therefore could not and did not rest on physical publication in a medical journal—Shaw-Mackenzie had priority there—but rather on the lecture that he gave to the EPC on December 13, 1904. This, and his subsequent lecture in Liverpool, formed the basis of his February 4, 1905 *Lancet* article. If we accept the fact that the Edinburgh and Liverpool lectures were virtually identical, then Beard deserved priority, if only by a few weeks. Such was the claim put forward by Beard and his supporters.

In response to this, Shaw-Mackenzie charged in the *Medical Press and Circular* that a pamphlet he had published in October 1904 gave him priority. Even before his January 1905 scientific publication, he said, "my work. . . was portrayed in my pamphlet, *Some Methods of Hypodermic Medication in the Treatment of Cancer* (October 1904)."[67] However, were trypsin injections really portrayed in this earlier work? If so, then Shaw-Mackenzie would unequivocally deserve priority. Only a single copy of this pamphlet survives today, in the Rare Books Room at Cambridge University Library.[67] I have obtained a photocopy of this work, but it contains no mention of pancreatic enzymes whatsoever. Shaw-Mackenzie thus seems to have overstated his case.

Priority to intellectual ownership of the concept of enzyme therapy of cancer is purely of academic interest today, but 100 years ago it caused a heated controversy and was even the subject of a *New York Times* editorial, which sided with the claims of Beard over those of Shaw-Mackenzie.

Shaw-Mackenzie also originated another idea that down the years has often been ascribed to John Beard. This was the notion that cancer arises because of a deficiency in pancreatic enzyme production, especially as a person ages, and that extrinsically applied enzymes were therapeutically useful because they rectified this deficiency. This later theory became second nature to 20th century Beardians. However, Beard himself neither originated nor accepted this concept. While it is tempting to dismiss Shaw-Mackenzie as an empiricist who tried a variety of odd-sounding cancer treatments (including Chian turpentine), to his credit he continued to investigate the use of enzymes for the treatment of cancer at various London research institutions for the remainder of his life.

The *Lancet* Controversy

Any pleasure Beard might have had in seeing his theory aired in the *Lancet* on February 4, 1905, was marred by the accompanying editorial in that same issue. A guest editorialist not only failed to support Beard's thesis, which would itself have been unusual, but took the occasion to lash out at Beard in a full-scale, vituperative personal attack: "Illogical reasoning. . . fantastic but seemingly logical superstructure. . . passes from one conjecture to another. . . not in accordance with known truths. . . launches into the realm of therapeutics. . ."[68] were just a few of the negative comments.

To this day the identity of the guest editorialist remains unknown. However, as one of Beard's supporters wrote: "There is internal evidence. . . which makes certain that the writer was himself a cancer researcher, and highly probable that he was the most prominent among such workers in Great Britain at the time."[40]

Readers have wondered why the *Lancet* editors chose to publish Beard's "illogical" and "fantastic" theory, and then simultaneously commissioned someone to attack it. The editorialist provided an answer that was quite extraordinary. Since the Carnegie Trust and the University of Edinburgh's Moray Fund had financially supported Beard's work, he said, it was incumbent on the *Lancet* to expose their misguided funding decisions! However, the sum total of the two funds' contribution to Beard's research had been £70, a minuscule amount even by the standards of the day. By contrast, the Imperial Cancer Research Fund (ICRF), of which the royal family was the chief patron, in 1908 had a capital endowment of £120 000. This issue of alleged funding irregularities seems to have been a pretext for attacking a theory of cancer that the writer found offensive. In the United Kingdom, the reception of Beard's ideas among the professionals who dealt with cancer was never anything but frosty.

C. W. Saleeby

Beard's 1902 article on cancer in the *Lancet* had come and gone, unnoticed. But in 1905 the *Lancet* article gained notoriety, thanks in part to the controversy generated by the aforementioned editorial. One of those who took notice was Caleb Williams Saleeby, MD (1878-1940), the son of a Lebanese merchant father and a native English mother, who had been one of Beard's medical students at Edinburgh. Saleeby had served a residency at the Edinburgh Maternity Hospital and was a fellow of the Edinburgh Obstetrical Society. In a highly unusual move, he had given up medical practice entirely and devoted himself to writing for newspapers and magazines about science and medicine. There had of course been physician-writers from the time of Hippocrates, even popularizers, but they almost always continued to practice medicine as their main profession. Saleeby, however, supported himself entirely by his newspaper and magazine articles on medical topics. He was therefore among the first full-time medical journalists. He is best remembered today for his spirited advocacy of eugenics and for coining the words "smog."[69]

Although Saleeby protested that his sole motive was human enlightenment, he had evidently concluded that his former professor could become a worthy *cause celèbre*. He therefore began a publicity campaign that resembled those of the contemporaneous American muckrakers. In February 1906, he wrote about the neglected "genius" John Beard in his "Scientific Notes" column in London's popular *Pall Mall Gazette*. In March, he produced a longer laudatory article for the American *Harper's Weekly*. A stream of similar articles followed in the *Daily Mail, Morning Post*, *Observer,* and *Contemporary Review*. In August, he published his most influential piece on the topic, "Cancer, Can It Be Cured?" in *McClure's Monthly*, an illustrated magazine published in both London and New York.[70] He claimed that Beard had reviewed and approved the article. In December 1906, after a well-known American physician, William James Morton, MD, had publicly confirmed Beard's therapeutic claims, Saleeby, in his own words, "threw caution to the winds." For the next year he created a whirlwind of interest in Beard and his theories on both sides of the Atlantic, culminating in publication of his book, *The Conquest of Cancer* (1907).[40]

However, quite in step with this, prominent British doctors began attacking both Beard and Saleeby with increasing rancor. Typical of the epithets thrown at Saleeby were "criminal," "brutal," and "irresponsible." A member of the medical profession had never before directly challenged the profession's leadership in quite this way. He was accused of encouraging patients to avoid surgery and resort to enzyme treatment instead, despite the fact (as he repeatedly pointed out) that he was a consistent and strong advocate of early diagnosis and treatment. In December 1906, the *British Medical Journal,* official voice of the British medical profession, censured him by name. The London *Medical Press and Circular* issued a vicious personal attack, and then demanded "an ample apology" from him!

These were time-tested measures for keeping recalcitrant members in line. And, prior to this, any doctor would certainly have been ruined by even a fraction of such public animosity from his esteemed colleagues. Most importantly, his source of referrals, and therefore his income, would have promptly evaporated. One only needs to read George Bernard Shaw's *The Doctor's Dilemma*, first performed in London in 1906, to get a glimpse of how stultifying British medical conformity could be. But times were changing. By choosing to make his career in the burgeoning world of medical journalism, Saleeby had found a niche that put him beyond the reach of his colleagues for either retaliation or censure. One gets the impression that he relished the notoriety.

Saleeby's 1907 book on Beard, *The Conquest of Cancer*, was published to generally favorable reviews. He appeared to be Beard's loyal and devoted follower. It is therefore quite surprising that a short while afterward there was a total break in their relationship. After 1907, he moved on to other topics, primarily the eugenics movement, and there is no sign that he ever returned to the topic of enzymes again. Conversely, turning to Beard's writings, there is no indication that a person named Saleeby ever played a role in his life. The break was therefore complete. One can only speculate on what the source of their disagreement may have been. For instance, Beard may have become uncomfortable with the promotional, even sensational, tone of Saleeby's writings. But without Saleeby, it is highly unlikely that Beard's theory would have become as well-known as it briefly did. It was mainly because of Saleeby, and his influence on American mass media, that by 1907, 1 in 6 American doctors reported using pancreatic enzymes in his practice.

Nobel Prize Nomination

The enzyme controversy did not immediately harm Beard's reputation. In 1906, he was even nominated for the Nobel Prize in medicine. The "motivation," as it was called, read as follows:

> The discovery of the existence in lower vertebrates of an independent nervous system which arises and is functional during earlier embryonic stages, the discovery of the true nature of the thymus gland, demonstration of the direct morphological continuity of the germ cells of vertebrate animals.[71]

The nomination did not mention his cancer theories, which were probably too controversial to be brought into

the deliberations. The nominator was Andrew Melville Paterson, MD (1862-1919), professor of anatomy at the University of Liverpool, who was among a small group of individuals asked by the Nobel Prize committee to propose possible award recipients. To be sure, Beard did not win, but just to be nominated was an honor he shared that year with such luminaries as Joseph Lister, Paul Ehrlich, and Eli Metchnikoff.

However, throughout the period of 1905 to 1909 there was an increasing amount of opposition to Beard's theory, particularly among British cancer surgeons. Although Beard's work was initially published in top British journals, he, Saleeby, and other supporters were personally attacked in the *Lancet,* the *British Medical Journal*, *Nature*, and other journals. Opposition was centered in the powerful ICRF. (In 2002, the ICRF merged into Cancer Research UK, now one of Great Britain's largest charities.) The Prince of Wales (the future King George V) was president of the ICRF, and early in the controversy he lent his name and support to a condemnation of John Beard.

Animal Experiments

Prior to this controversy, the idea had emerged of first testing putative cancer treatments in animals before applying them to human patients. A few animal models existed, such as Jensen's transplanted sarcoma, which was the first and best-known experimental mouse cancer system. In November 1905, Beard supervised the inoculation of 7 or 8 mice with Jensen's sarcoma. After about 5 weeks, these mice developed tumors. Two were then injected with trypsin. Beard observed a complete degeneration of the tumors in these animals. On January 20, 1906 the *British Medical Journal* published Beard's article on his experiment.[72]

Since the *British Medical Journal* was the official organ of British medicine, this publication carried great weight in the English-speaking world. But the article was followed by a furious reaction from the Royal College of Surgeons of Edinburgh. They questioned the validity of this animal model and also attacked Beard because they claimed that he had stated, without their explicit permission, that the experiment had been performed "in the research laboratory of the Royal College of Physicians, Edinburgh." Beard's coworker in this experiment, Dr Henry Wade, did indeed work for the Royal College, but this was not an officially commissioned experiment.

Immediately thereafter, the *British Medical Journal* (as well as some other United Kingdom medical publications) refused all further articles on cancer by Beard. At the same time, the Prince of Wales announced that the ICRF had tested trypsin in a much larger group of animals, using a variety of tumor types, and had uniformly failed to attain any positive results. This was a crushing blow, which had repercussions as far away as Germany and America. The trouble was that these results were never formally published. One was expected to simply take the Prince's word for their veracity, since the future King would obviously never lie. On January 10, 1906, writing in *Nature*, Beard called on the Prince and the ICRF to publish details of their experiment. But this they persistently refused to do. So while Beard and the rest of the world saw summaries of their experiments, which were presented at scientific meetings and in the general press, there never was a peer-reviewed scientific publication.

Beard raged at his inability to critique these supposedly damning results and came to doubt their intrinsic honesty. "It is no refutation," he later wrote, "to take a solution labeled 'trypsin,' and then, after injecting it in vain into a mouse with a tumor 'about as big as itself,' to declare that trypsin had no action on cancer cells." The therapeutic agent in question, he continued, should have been tested ahead of time to verify that it had activity. He called the ICRF's preparations "supposed, but fictitious, ferments." Adopting a combative tone worthy of his mentor Huxley, he concluded:

> There would appear to be no valid reason for the continuation of such sterile institutions (as the ICRF, ed); they might just as well, for the sake of economy, be closed, and the official salaries be paid to the holders of the appointments, without asking them to 'test' the action of substances, such as trypsin. . . .[73]

The trypsin controversy also exposed class divisions in British medicine. Beard won the support of many nonspecialist physicians. Their journal, the *General Practitioner,* supported Beard with five articles and editorials. By contrast the elite *British Medical Journal*, which also had a dozen reports on the treatment, was generally hostile. This divergence of opinion reflected the gulf between the general practitioners, who welcomed the opportunity to treat a growing number of cancer patients, and the specialists, who treated cancer with surgical operations of increasing complexity. This gulf between general practitioners and specialists was one of the themes of Shaw's *The Doctor's Dilemma* (first staged in 1906).

F. W. Lambelle

In 1906, Beard first met a person who was to play an important role in his subsequent life. Captain Frederic William Lambelle (1873-1951) became his closest friend and colleague. Born in Weston, Durham, on December 9, 1873, Captain Lambelle was the oldest son of William H. Lambelle, who was a journalist and newspaper editor. Captain Lambelle received his medical degree from

Durham University and shortly afterwards was commissioned as a lieutenant in the Royal Army Medical Corps. In 1902 he was sent as a military surgeon to Hong Kong, where he remained until January 1906. While there, in addition to his surgical duties, he also taught physiology at Hong Kong College of Medicine.[74]

In 1904, one of Beard's papers on germ cells found its way to Lambelle in China. "These findings interested him so much that he endeavored, on human embryos, to make independent observations," Beard later wrote. In 1905, Lambelle was ordered home and, on reporting to the Director General of the War Office, mentioned his interest in Beard's research. He was thereupon stationed with the 2nd Light Dragoons (The Royal Scots Greys), which at that time were garrisoned in Edinburgh, primarily so that he could meet Beard.

Here is how Beard described their first encounter in January 1906:

> From the day when, unannounced, Captain Lambelle entered my little room in full uniform, and, saluting, introduced himself, we have been close friends. He worked for himself over much of my material—a collection also, like the Scots Greys, "Second to None!"—and he read all my published papers, which, unlike some scientific people, he thoroughly understood and appreciated; in fact, he evinced the deepest interest in all the problems and their solutions which had occupied my leisure hours during many years.[20]

Later that year, Lambelle was assigned to the military hospital in York, several hundred miles away, but the two stayed in touch. In 1907, together, they announced the first apparent cure of cancer with enzymes in the *Medical Record*. This was the case of "Signora S." of Naples, whose inoperable tongue cancer was treated with enzyme injections at the provincial hospital there. Lambelle and Beard served as scientific advisors to the treating physicians, Gennaro Cavaliere Guarracino, MD, physician and surgeon to the provisional hospitals for the insanes of Naples, and to the Hospital of St Eligio, and Professor Michele Manzo, MD, surgeon to the Pilgrims' Hospital there.[75]

Lambelle's army job was to tend to the surgical needs of young soldiers. Needless to say, these men were unlikely to have cancer, a disease that, then as now, predominantly afflicted older people. However, in October 1908, he had the opportunity to administer enzymes to a "Yorkshire lady of social position," as he described her, who had been diagnosed with breast cancer. Although Lambelle and other doctors made the diagnosis by clinical examination, no biopsy was taken. (The necessity of biopsy was not then firmly established.) Two years later, the woman was still alive and free from recurrence "as near as mortal man can say 'cured,'" claimed Beard, although some critics faulted the case for the lack of an objective, independent pathological diagnosis, confirmed by histology.

In March 1909, Lambelle began to treat "W. Du T.," a retired drummer in the 4th Battalion of the West Yorkshire Regiment, with trypsin injections. "The tumor was recurrent immediately after two operations upon it, and it had become inoperable," Beard later wrote. This time, "the diagnosis was confirmed by microscopical examination of a portion of the tumor mass removed at the second operation by a pathologist of the Royal Army Medical College…. The diagnosis given is not open to the slightest question." The ex-drummer had a complete remission of a recurrent round cell sarcoma of the left upper jaw. Lambelle wrote the case up for the *Journal of the Royal Army Medical Corps*[76] and Beard reprinted and discussed it in his 1911 book. Indeed, he later stated, with some exaggeration, that the main purpose of that book was to provide the medical profession and the general public with documentation on this exemplary case![72] It "demonstrates for all time the scientific truth" of the trophoblastic theory, Beard proclaimed. The patient was still alive and well when Beard published his book, 2 years later, and he speaks of him as cured in his final 1919 paper.[73] This was the case that convinced Beard, and some others, that his theory was essentially correct. He considered it to be a scientific proof of principle, against which no number of negative cases could stand.

But this case was not alone. Reports on the effects of trypsin therapy—both positive and negative—continued to accumulate, so many that in April 1907, a writer in the *Morning Post*, disguising himself simply as "FRCS," (ie, Fellow of the Royal College of Surgeons) demanded the appointment of a Royal Commission to look into enzyme therapy. "The uniformity of beneficial results has been remarkable," he wrote.[40] The fact that, apparently, a British surgeon held such opinions but was afraid to give his name itself speaks volumes about the climate of the times. Beard claimed that other doctors were also using the treatment with success, but, like "FRCS," were afraid to report it: "In addition to these cases," wrote Beard, "there have been others which were not published, usually because the physicians concerned did not see fit to submit themselves to ridicule and abuse for writing the truth."[20]

After the negative ICRF pronouncement, those who still attempted to defend Beard's trophoblastic theory were characterized in the *Lancet* as "persons who persist in advocating its use by repeating stories of alleged 'cure' when. . . the patients. . . died from the disease."[20] In other words, the authorities had spoken, and this fact alone, and no number of facts to the contrary, meant an end to this possible way of dealing with cancer by nonsurgical means.

In December 1907, Charles C. Scott published a case report in the journal *General Practitioner* on the successful treatment of a cancer of the caecum with enzymes, whereon the operating surgeon, Professor Albert Carless (1863-1936) of King's College, London, appended a note saying that he now doubted his own diagnosis! His

reasoning was that since the treatment in question was worthless, the diagnosis itself must have been faulty, since the patient recovered.

J. Aspinall Marsden, MD, followed this, on January 11, 1908, with an article in the same journal on the successful treatment of a woman with carcinoma of the uterine cervix. Dr Henry Meggitt also treated a total of six patients. "In all cases I have seen," wrote Meggitt, "I have not yet met with one that has not obtained benefit." In particular, he reported on a "cure" over a period of 7 months of a recurrent liver cancer using pancreatic enzymes (*General Practitioner*, March 21, 1908).[40]

In January 19, 1907, the *British Medical Journal* also published a highly negative article on enzymes and one week later reported on the general superintendent of ICRF's adverse comments on Beard and enzymes. This article pointedly failed to mention the many positive cases that had been reported in foreign journals.

The condemnation of trypsin came in the name of the president of the ICRF, the Prince of Wales. Although it is doubtful that the future King George V knew or cared much about John Beard, his endorsement of the ICRF conclusions swayed many casual observers to adopt a negative stance toward the new treatment. In a letter to *Nature,* Beard immediately challenged the ICRF to release details of its animal experiments. It was a reasonable request, but was never done. The ICRF's final condemnation came in an in-house publication, the *Third Scientific Report of the Imperial Cancer Research Fund,* which was published in 1908. By doing so, the ICRF violated long-established scientific protocol and provided Beard (and others) no opportunity to critique their methods or results as they had been able to critique his. But it was the authority of the ICRF that was of paramount importance here. This upstart from Edinburgh had challenged an august and wealthy medical institution. The institution then reasserted its authority, using the prestige of the royal family to reinforce its case. This was the reason that, toward the end of his life, Beard bitterly complained: "There is no generally recognized criterion for truth in science—except human authority!"[77]

At the very height of the enzyme controversy, Beard suffered a personal tragedy. On November 25, 1907 his German-born second wife, Helen von Roschmann Beard, died. She was buried beneath a pink limestone gravestone in nearby Comely Road Cemetery. Helen was 43 years old (see Figure 3).

Figure 3. The Grave of Helen von Roschmann Beard and John Beard.

Support on the Continent

For many years, Germany had been the world center of cancer research. In the 1830s, Johannes Müller (1801-1858) had pioneered the microscopic analysis of malignancies and had shown that tumors are derived from normal cells. In the 1860s, Rudolf Virchow (1821-1902) in Berlin, developed the theory of cancer as being caused by local irritation. His student, Julius Cohnheim (1839-1884) introduced a theory that cancer arose from so-called "embryonal rests" (a theory even today that is often confused with Beard's own.)[78] Germans also pioneered transplant research and were among the first to propose the role of hormones in carcinogenesis. In 1902, the pathologist Max Borst (1869-1946) classified tumors according to their histogenesis,[79] basically the same method used today by the World Health Organization.[77] The first world cancer congress was held in Heidelberg in 1906. (Enzyme therapy was a topic of lively discussion there.)

Beard had received his doctorate from Germany, had twice married German women, had published steadily in leading German publications, and sprinkled his lectures and articles with German idioms. He was naturally regarded as an expert on German science. But all this occurred at a time of rising tension between Britain and Germany, which eventually led to the catastrophe of World War I. Stung by the rejection of his paper by the Royal Society, Beard understandably sought support for his views from his continental colleagues. In this, he wasn't disappointed.

In 1905, the German pathologist Ludwig Pick (1868-1944), wrote in a Berlin medical weekly and gave support to Beard's trophoblastic theory of cancer. In April of the same year, Ferdinand Blumenthal (1870-1941), director of the Cancer Institute in Berlin, published an article, "The Chemistry of Cancer," in which he showed that trypsin dissolved cancer cells. Beard personally translated this for the *Medical Press & Circular*.

Beard also apparently attended the cancer congress which took place in Berlin on March 8, 15, and 22, 1905, and which he reported on in the *Lancet*. Beard felt that not just Blumenthal, but also Professor D. von Hansemann supported his cause.[80]

In September 1906, at the First International Congress for the study of tumors and cancers in Heidelberg, Blumenthal repeated his claims concerning the carcinolytic properties of enzymes: "The tryptic ferment (ie, pancreatic enzymes) very easily dissolves the cancer cells, while the very opposite is the case towards the other tissues," ie normal cells.[81] But, after the ICRF publicized its own negative animal studies, Blumenthal reversed himself and concluded that enzymes must be clinically ineffective. Beard expressed disappointment in this, since Blumenthal's about-face was not based on a proper publication that could be scientifically critiqued.

There were also positive reports on the use of enzymes from workers at the Pathological Institute in Berlin. In 1907, A. Pinkuss and S. N. Pinkus (1868-1947) showed that large doses of trypsin injected into healthy dogs were harmless and eventually were excreted in the urine. (Pinkuss and Pinkus were also the first to raise the issue that injections of trypsin might thereby create "anti-trypsin" in the animals.[82])

In addition, in July 1907, Professor August Bier (1861-1949), famous as the initiator of spinal anesthesia, supported Beard's use of enzymes in cancer in a German medical weekly, the first prominent surgeon to publicly do so. For Beard, the high point in terms of his German support came in 1907, when Ernst Viktor von Leyden (1832-1910), professor of clinical medicine, University of Berlin, and head of the officially subsidized cancer research establishment, and his assistant Peter Bergell, confirmed that enzymes had a specific digestive and toxic action on cancer cells. Von Leyden, personal physician to the Russian Czar Alexander III, was generally considered the world's greatest authority on cancer.[83]

There was a perception that the enzyme treatment had taken root in Germany. In 1908, a spokesperson for the Glasgow Cancer and Skin Institution reported in a newspaper that the enzyme treatment "is being adopted in Germany, with excellent results."[84] In private, Beard doubted its widespread use there and was contemptuous of the quality of the enzymes available on the continent at that time. However, starting in 1906, Beard was flooded with requests for enzymes and for instructions on their use, not just from abroad but from physicians and hospitals in Britain as well.

This put him in an awkward position. As a doctor of science, a "mere" biologist, he was treading a fine line. He wanted to convey his scientific understanding of enzymes without being perceived as telling physicians how to treat their patients. He routinely deferred to physicians, such as his former fellow student, Dr Robert Maguire, FRCP, Senior Physician at Brompton Hospital, who advocated intramuscular injections. Beard's own inclination from the start was to give the injections intravenously, although most doctors at the time administered them in less rapidly absorbed forms. However, the principle was that as a non-physician, Beard had to leave treatment "in the hands of those who know far better how to employ it," or risk being branded a quack.[73]

Beard himself could therefore do little more than provide correspondents with general guidelines. He took the position that those most skilled in providing treatment should be left to work out the therapeutic details, once he had pointed out the basic scientific principles.

Other European Countries

There were also reports from other European countries on the successful use of enzymes in cancer. For instance, Dr Louis Odier of Geneva, Switzerland, reported in *La Presse Médicale* that he had found a pancreatic enzyme deficiency in strains of mice, which developed spontaneous tumors. He then treated these animals with enzymes and in every case their growths were arrested. He published "The Treatment of Malignant Tumors, and of Tumors in Process of Development, by the Injection of Glycolytic Ferment," in *Médicine Orientale*, a publication of the French Academy of Science. He later discussed his preliminary results in humans, which he also found very encouraging. (From internal references, however, I conclude that Odier was more influenced by Shaw-Mackenzie than he was by Beard.)

In Italy, in March 1906, G. Zanoni, director of the Instituto degli Ospidali e della Cliniche, published a positive animal experiment with enzymes in *Gazzetta degli ospedali e della cliniche*. (This was reported in the *Journal of the American Medical Association*.) As mentioned, in January 1907, Beard and Lambelle reported in the *Medical Record* on the first apparent cure of cancer using pancreatic enzymes. This was the case of Signora S. of Naples, who had an inoperable cancer of the tongue. Cavaliere Gennaro Guarracino, physician and surgeon to the provincial hospital, and three other Italian doctors treated her with enzymes. Also in 1907, Dr Mario Donati published an article in the *Riforma Medica* on the cure of a malignant tumor with injections of trypsin.

Reception in the United States

On the whole, Beard's theory was received with respect, even enthusiasm, in the United States. In fact, the majority of positive reports on the efficacy of enzyme therapy came from the United States. After he was effectively blocked from publishing on cancer in major British journals, Beard increasingly turned to their American equivalents. For years, the New York *Medical Record* served as a kind of "house organ" for enzyme therapy. In March 1906, Saleeby published a long article on Beard's theories in *Harper's Weekly*, in which he rashly called trypsin "a veritable cure for cancer."

This claim of course went way beyond what could be supported by the facts at the time and, predictably, triggered many comments, including the first of three-dozen articles and editorials in the *New York Times* (March 6, 1906). *The Times* referred to Beard's "remarkable but practical theory" and said that it offered comfort to all those suffering from "cancer-phobia." The *Journal of the American Medical Association* also published three accounts of successful enzyme treatment. But an anonymous editorialist warned: "It is evident that this kind of exploitation of the trypsin treatment of cancer should cease. It is not at all creditable to its advocates."[85]

In February 1907, W. Roger Williams, MD, the author of several cancer textbooks, attacked Beard's theory in the New York *Medical Record*. He argued that since people sometimes developed pancreatic cancer, and the pancreatic gland produced enzymes, then *ipso facto* Beard's theory that enzymes destroyed cancer cells must be wrong. This argument ignored the fact that the pancreas does not produce trypsin, but only its inactive zymogen form, trypsinogen. This proenzyme is then normally channeled into the duodenum where it is converted to its active form through the presence of enterokinase.[86]

This was known at the time. A contemporary textbook stated, as a well-known fact, that trypsin "and other pancreatic enzymes do not exist as such in the gland cells. These. . . contain the zymogen, and neither the secretion nor an extract of the fresh pancreas has any proteolytic action."[87] Thus there would be no particular supply of enzymes present within the pancreas available to fight appearance of tumors. It is surprising that a doctor of Williams' standing would make such an elementary mistake. Nevertheless, this specious argument was subsequently repeated many times as a supposed refutation of Beard's theory.

What were the practical results in contemporary cases treated with pancreatic enzymes? Clarence Rice, MD, of New York published the "first important case"[88] in November 1906. Rice reported on a cure of advanced cancer of the larynx, with the patient alive and well nearly one year after beginning on the enzymes. "This treatment exerted a very prompt action upon the growth," Rice reported.[89]

In December 1906, William James Morton, MD (1845-1920), son of the codiscoverer of ether anesthesia, reported on 29 advanced cancer cases treated with pancreatic enzymes over an 8-month period.[90] All were deemed beyond help at the beginning of the treatment. Although Saleeby stated that the doses Morton administered were far too small, nevertheless, 2 patients with facial cancer were allegedly cured, and two other patients had their malignant lymph nodes shrink. In 5 cases the enzyme injections produced constitutional reactions such as fever, rigor, etc, that were reminiscent of another controversial treatment of the day, Coley's toxins. In 4 cases it also produced swelling, heat, pain, or increased discharge in the tumor itself. In 2 cases the disease was "brought to a halt" (ie, stabilized) although the treatment in the end did not prove curative.

Morton added an additional case in the *New York Medical Journal* of March 1907. This patient had 2 operations and had returned in September 1906 with 2 metastatic nodules under the chin. He was treated for 10 days with enzymes. The growths entirely disappeared and there was no sign of recurrence 3 months later when Morton wrote up the case. Morton's famous name carried weight. In March 1907, however, the *British Medical Journal* published Dr William Seaman Bainbridge's claim that one of Dr Morton's cured cases had relapsed and died. Opponents of the treatment "arousing in various hostile quarters a chorus of the most malignant delight," seized on this gleefully, said Saleeby.[40] Meanwhile, Morton added another successful case in the *New York Medical Journal*, but in the inflated controversy over his single erroneous case, this was ignored. The erroneous case was used to paint him as a liar and to discredit his entire testimony concerning enzymes.

In December 1906, the surgeon F. B. Golley, MD, a graduate of the University of Michigan Medical School, published in the *Medical Record* 2 cases of cancer treated by the injection of pancreatic extract. Also, Frederick Wiggin, MD, read a paper before the Society of Alumni of Bellevue Hospital, New York, on a single case of fibrosarcoma of the tongue treated with trypsin and amylopsin (amylase). This was published in the *Journal of the American Medical Association*.[91] The *Journal of the American Medical Association* published a second positive case, by W. H. Rogers, MD, of rectal cancer, in December 1906,[92] and in March 1907 another "report of a cure" by Richard A. Goeth, MD, of San Antonio, Texas.

Beard was riding high. In February 1907, the *New York Times* lauded him in an editorial: "There is probably today no better equipped man teaching embryology than Dr Beard."[93] In the same month Dr Luther of the University of Pennsylvania published a preliminary report in the *New York Medical Journal* on his use of enzymes. He concluded that it caused: "(1) arrest or shrinkage of the growth; (2) improvement in the general health;

(3) diminution or cessation of pain; and (4) diminution of the discharge. . . ."[94]

In June 1907 John G. Clark, MD, discussed the trophoblastic theory in *Progressive Medicine* of Philadelphia. Clark called it "the most startling as well as most unique theory."[95] That same month, Margaret Abigail Cleaves, MD (1848-1917), one of America's most prominent female physicians, enthusiastically endorsed Beard's work in "The Physiologic Action of the Pancreatic Enzymes" in the *Medical Record*. In the following month, Homer Dupuy, MD, a surgeon at an eye, ear, nose, and throat hospital published a complete response in a case of laryngeal epithelioma in both the *New Orleans Medical and Surgical Journal* and *The Laryngoscope*. The author gave intramuscular injections alternating with an oral enzyme preparation called Holadin. Within three months the growth disappeared entirely.[96] Five laryngologists and a competent pathologist signed off on Dupuy's case. A New York author called the results "brilliant and satisfactory."[97]

In October 1907, *American Medicine* editorialized that John Beard "has described his work and conclusions in such a dogmatic and egotistical way as to give a very unfavorable impression as to the reality of the things he thinks he has discovered. . . ." Yet despite this unfavorable assessment of his personality, *American Medicine's* editors concluded, "That he has made an addition to our knowledge of cancer no one need doubt." Noting his increasing difficulties in the United Kingdom, they added, generously, "The prophet is without honor in his own country, so that the English adverse opinion may in reality be proof of the opposite."[98] Despite a bad case of the jitters on the part of his publisher, Caleb Saleeby managed to get *The Conquest of Cancer* published in November 1907 in both Britain and America. It almost didn't happen. At the last minute, the publisher, Frederick A. Stokes & Co, demanded a delay in publication for further fact checking because of the mounting criticism in top medical circles. Things descended from this high point very quickly thereafter.

William Seaman Bainbridge, MD

In September 1906, Beard received a visit at his Edinburgh home from William Seaman Bainbridge, MD (1870-1947), a surgeon at the New York Skin and Cancer Hospital, New York (long since merged into University Hospital). Bainbridge, a young man with large ambitions, was visiting Europe to attend the First International Congress for the Study of Tumors and Cancers in Heidelberg. In fact, at age 36 years old, he was already the honorary president of that congress.

Bainbridge proposed an extensive American clinical trial of enzyme treatment. Whatever reservations Beard may have had, he could hardly say no. At the congress itself, Professor Blumenthal of Berlin had praised enzyme treatment, saying "the tryptic ferment very easily dissolves the cancer cells, while the very opposite is the case towards the other tissues," ie, normal cells.[40] However, Bainbridge did not have such a positive opinion of enzyme therapy. Within a few months, on March 2, 1907, he issued the first of several derogatory articles on the "trypsin treatment of cancer" in the *New York Medical Journal*.[61]

In 1909, Bainbridge, speaking for his hospital's Committee on Scientific Research, published a 39-page pamphlet on "The Enzyme Treatment for Cancer." This report claimed to demonstrate the failure of Beard's enzyme treatment in 100 cases of "terminal" cancer treated over a 3-year period. He found no curative value in the treatment itself, and contrasted his own results in 100 cases with the single case of the ex-drummer that supposedly supported Beard's claims.[99] The Bainbridge report, Beard later said, was "scattered broadcast" around the world and undoubtedly did irreparable damage to enzyme therapy.

Although Bainbridge did note some palliative effects of the treatment, including a liquefaction of tumors at injection sites, he emphasized that none of his patients was cured. Thus, the positive aspects of the study were far outweighed by the negative conclusions that Bainbridge himself drew from the work. This was a most serious blow to Beard's credibility. Beard did not dispute that these cases were essentially failures, but he said that enzymes were not the medical equivalent of the last sacrament, ie, something to be given when all else had failed and the patient was at death's door. Nor were they in the nature of a "magic spell or incantation." In other words, patients who had been put through extensive prior surgery and were in a state of cachexia could not be brought back to health with a few digestive enzymes administered at the last moment.

Second, there was great inconsistency to commercial products labeled "enzymes." P. T. Hald had indeed demonstrated in 1907 a huge variability in the strength of enzyme preparations.[100] Many of these products were even deceptively labeled and were deficient in their chemical composition, purity, and potency (a problem that persists a century later). Preparations that contained glycerin and water, with at most a trace of enzymes, could hardly be expected to work miracles in terminal patients.

Finally, Beard concluded that the means of delivering the enzymes also had a great bearing on their effectiveness. Under the influence of some physicians, enzymes were usually administered subcutaneously or at most intramuscularly. But Beard believed that the most effective means would be through intravenous administration. Most clinicians were too afraid to do this, but 10 years later, M. W. McDuffie, MD, of New York, introduced this mode of administration.[101] Decades later this was the same mode of administration favored by another American physician, Frank L. Shively, of Dayton, Ohio, until the

treatment was eventually banned as an unapproved medication by the FDA in the 1960s.

Pancreatic Enzymes and Malaria

In January 1911, Beard's friend Captain Lambelle, was ordered to upper Burma as a specialist in advanced operative surgery of the 5th Mhow Division. He stayed there for two and a half years. In the summer of 1913, Lambelle was sent home on sick leave. He recuperated in Scotland at Beard's home on Barnton Terrace. In the meantime, in August 1914, World War I broke out. A year later, at a time of national crisis because of the unsuccessful invasion of Gallipoli, Lambelle requested permission to rejoin his unit full time. He did this and in 1917, he was decorated for military service and promoted to the rank of Major. (For reasons unknown, in 1912, Lambelle started spelling his name *Lamballe*. To avoid confusion, I will stick with the earlier spelling.)

The nature of Lambelle's recurring illness is unknown but the facts are consistent with chronic malaria. In support of this idea, Lambelle's only extensive scientific article in this period was the report of a clinical trial of the use of enzymes in the treatment of malaria.[102] Malaria had been nearly universal among British soldiers in Hong Kong during his tenure there, and was common in British India and Burma as well. Beard followed Lambelle's clinical trial with an article of his own on the same topic with a former student, the tropical disease specialist Andrew Balfour of Khartoum (1873-1931). This was published in the *British Medical Journal* during World War I—his only publication in that journal after he was shunned by it at the height of the cancer controversy.

In 1919, Beard reiterated,

> Relapsed malaria is one of the simplest and easiest diseases to treat and cure by injections of pancreatic ferments. . . . Nonetheless, during the recent war, it was impossible to convince the War Office and the Royal Army Medical Corps that in the treatment of malaria there was any scientific alternative to quinine.[73]

After the war, however, Major Lambelle's ill health returned and in April 1921 he took early retirement. He survived another 30 years and died in York on May 5, 1951, at age 77 years old.

The Enzyme Treatment of Cancer

In 1911, the respected firm of Chatto & Windus of London published Beard's one full-length book, *The Enzyme Treatment of Cancer*. A Chicago edition followed in the following year, although neither sold particularly well or generated much attention. The book itself was an annotated and expanded version of Beard's previous articles on cancer. Although obviously convinced of the merit and inevitability of enzyme therapy, Beard at times adopted a valedictory tone, as if he realized that he was now writing mainly for posterity.

After the book's publication, Beard largely fell silent. In the decade after 1911, this once prolific researcher published just 4 articles. His last publication in a German journal occurred in 1913, just before the outbreak of war between his native country and his intellectual homeland. His final paper, a spirited defense of the trophoblastic theory, appeared in the *Dublin Journal of Medical Science* in 1919.[73] In 1911, Beard had challenged the medical profession to subject the case of the ex-drummer to intensive scrutiny. Eight years later he revealed that not a single medical doctor had asked to see the charts, photographs, and the diagnostic slides of the man's tumor. (One medical student did ask, but after reviewing the slides, left without further comment.)

In this last article (1919), Beard was defiant: "Of the essentials, I have nothing at all to withdraw. Indeed, these ferments, properly and scientifically employed, are. . . the sole possible scientific treatment for cancer," he wrote.[73]

It is worth noting that during this time, Beard and others also advocated the use of pancreatic enzymes in the treatment of tuberculosis. Harry Edwin Lewis, MD, of Burlington, Vermont, was a prominent American pulmonologist who used hypodermic injections of enzymes in tuberculosis. His example was followed quickly by German doctors, but that too eventually fell by the wayside.[104]

Initially, Beard had told friends that his cancer work was a diversion from his basic research in embryology, but he never returned to his former areas of specialization. According to *Nature*, Beard's cancer work "eclipsed his interest in his earlier lines of work, but his coworkers in zoology always continued to hope. . . that his profound knowledge of the details of development of elasmobranchs, and especially of the skate (*Raja*), would be made available by publication to future writers." Beard's motives for proposing a solution to the cancer problem were scientific and humanitarian. But by so forcefully putting forward his views he managed to estrange the medical profession, while simultaneously disappointing many of his scientific colleagues.

In the 2 years following the publication of his 1905 article, with reports of success coming from various sources and countries, victory over medical intransigence must have seemed a distinct possibility. But the forces arrayed against Beard were far too great to be easily defeated. The establishment, through the ICRF and Bainbridge reports, readily overcame Beard and his cohorts, and the public moved to other treatments (such as the radium "cure" of Mme Curie).

Without Dr Saleeby's tireless efforts on his behalf, the world soon had forgotten John Beard, trophoblasts and trypsin. Most people who were still interested would probably have consulted Bainbridge's popular 1914 book, *The Cancer Problem*, which contained a recapitulation of the author's negative experiences with enzymes. Unlike Beard's book, Bainbridge's was critically acclaimed and was translated into French (1922), Spanish (1927), Italian (1933), and even Arabic (1935). Thus, for most readers, John Beard's theories were filtered through the writings of his most determined opponent.

Later Years

We know little about Beard's later years. He served as the director of a large buyer's cooperative that was loosely affiliated with the university staff. We know that at some point, he married for a third time, to a woman named Florence Sedgley, but all details of this marriage are unknown.

In 1920, John Beard's health began to deteriorate, most likely because of progressive cardiovascular disease. In 1921, he took early retirement from the university and spent his final 3 years at home. His retirement was announced without comment in the local newspaper. There was no mention of any celebrations.[105] Throughout 1924, signs of steady improvement encouraged his friends and family. But on November 24, 1924, Beard suffered a stroke, and on Tuesday, December 2, at precisely 9:10 AM, he died at his home at 8 Barnton Terrace. He was 66 years old.

On Friday, at 2:30 PM, John Beard was buried in Comely Bank Cemetery, next to his second wife, Helen. Today, they share a pink granite gravestone, beneath what is now a towering cypress tree (see Figure 3). His portion simply states "Also John Beard, DSc" with his birth and death dates. The interment took place in a drenching rainstorm and there was a simple two-line announcement of his death and funeral in *The Scotsman,* "Outdoor conditions were the reverse of pleasant," the weather report noted.

The only full-scale obituary was in the British journal *Nature*. This was anonymously written, but contained intimate details on Beard's life and health that could only have come from his son or from a close Edinburgh colleague, such as his department chief, James Cossar Ewart. Other than that, his death went largely unnoticed, even by journals to which he had frequently contributed in the past. A few brief mentions were all he received, such as this note in the American journal *Science*: "The deaths are also announced of the following scientific men: Dr John Beard, lecturer in cytology and comparative anatomy at Edinburgh University…"[88]

Did Beard leave any descendants? We do not know. His son Edgar, as a young man, was a member of the Scottish Mountaineering Club and a contributor to various photography magazines. He graduated with a bachelor's degree in the "pure sciences" (ie, Geology, Physiology, and Mathematics) from the University of Edinburgh in 1914. He probably served in World War I. Thereafter, he followed in his father's footsteps, academically. He studied the pineal gland under a grant from the Carnegie Trust and in 1922 became lecturer in physiological chemistry at the University of Aberdeen. He later taught biochemistry as well, but does not seem to have published in the field. He took an early retirement from Aberdeen in 1940, at age 55 years old, and lived in the Western suburbs of Bieldside. Sometime after 1947 he stopped having an Aberdeen telephone directory listing, but I have been unable to locate any further information on his personal life.

Conclusions

Even before his death, John Beard's theory of cancer had been largely forgotten or else seriously misrepresented. In James Ewing's monumental textbook, *Neoplastic Diseases* (1922), there is but a single sentence devoted to Beard and it is misinformed. Ewing stated: "The usual integrity of the pancreas does not favor the theory of Beard that cancer depends on defective pancreatic secretions."[106] Not only did Ewing fail to cite Beard's writings, but clearly ascribed to him views that he never held. Whereas a younger John Beard generally responded to misstatements about his work, by 1922, his health was too precarious for him to respond in any way.

After his death, a handful or researchers passed along the idea that there had once been an enzyme treatment of cancer.[107] One can even trace a nearly continuous use of enzymes particularly in Germany and America. But it was mainly the existence of the book *The Enzyme Treatment of Cancer* that kept his ideas alive, however tenuously. Over the next few decades, odd copies of the book occasionally fell into the hands of individuals (such as Ernst T. Krebs, Jr) who were sufficiently intrigued to investigate its central concepts.

It was decades after Beard's death that mainstream researchers finally rediscovered the fundamental resemblance of trophoblast to cancer, although this discovery was usually advanced without any acknowledgment of its intellectual parentage. Similarly, it took decades for the biological activity and therapeutic potential of digestive enzymes to be confirmed by the academic research community, often without acknowledgement of Beard's pioneering work in this field. Today, John Beard is sometimes recognized as a pioneer of the CSC concept, apoptosis,

and the role of the thymus as an organ of immunity. However, in a larger sense, his fundamental contribution to cancer remains to be acknowledged or understood by the greater academic community.

Acknowledgments

I would like to thank the following for help with this article: David Cantor, PhD, National Library of Medicine; Frederick B. Churchill, Indiana University, Bloomington; Liz Cooke, Alumni Relations, University of Edinburgh; Irene Ferguson, Special Collections and Archives, University of Edinburgh Library; Nicholas Gonzalez, MD; Yvette Gunther, King's School, Chatham; Helen Hills, the University of Cambridge Library; my niece Jacqueline Kavanagh for photographs of Beard's gravestone; Jamie Love, PhD; my research director, Louise Lubetkin, DDS; Jacques Miller, MD, PhD, DSc, FRS, Walter and Eliza Hall Institute of Medical Research, Melbourne; Josef Novak, PhD, Bucknell University; and Peter Starling, British Army Medical Museum. Any remaining errors are solely the author's responsibility.

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