

## Injection, Ligation and Transplantation: The Search for the Glandular Fountain of Youth

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**Purpose:** During the 19th and early 20th centuries there was great interest in antiaging remedies. This search for the eternal fountain of youth stemmed from the concept of aging as a pathological condition that destroyed the body and mind. In addition, great emphasis was placed on the economic challenge that the elderly presented to society. We examine the history of antiaging therapies from the perfection of cell nutrition to glandular transplants.

**Materials and Methods:** A literature review was performed including direct first person sources such as historical documents, letters of correspondence, newspaper articles and journal publications. Historical texts were also consulted for accuracy.

**Results:** The history of antiaging medicine includes a variety of remedies. E. Metchnikoff advocated a diet rich in lactic acid which he thought would eradicate the body of intestinal putrefaction and decay. Others believed the fountain of youth lay within the endocrine system. C. E. Brown-Sequard linked the decrease in sexual function with the aging body and claimed he could restore a youthful state with the injection of a mixture of animal sex glands. The compound Spermine was subsequently marketed as an injection that promised the effects observed by Brown-Sequard. The early 20th century was marked by a number of surgical attempts at the restoration of youth. L. L. Stanley reported on more than 643 inmates at the San Quentin prison on whom he had performed testicular transplantation. This idea of gland grafting gained international interest and led others such as S. Voronoff to experiment with the transplantation of various animal glands into humans. In addition to gland grafting, vasoligation was advocated by E. Steinach in an effort to direct sperm from the testicles back to the body. The Steinach operation was claimed to restore youth and vigor. Although most physicians directed their attention toward remedies for men, some came to advocate remedies for women including ovarian transplantation and radiation.

**Conclusions:** The search for the glandular fountain of youth ultimately led to the discovery of testosterone. The modern day interest in plastic surgery, testosterone replacement and growth hormone injection underscores the concept of aging as a disease process. We have yet to determine whether aging represents physiology or pathology. However, it is certain that the search for the fountain of youth will continue.

*Key Words: hormone replacement therapy, androgens, testosterone, transplantation, aging*

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What is it about being human that prevents us from accepting the eventuality of aging? Is it fear of our own mortality or of outliving our usefulness? While the answers to these questions remain elusive, there is benefit in their ponderance as they form the scaffolding of the antiaging movement. The roots of this movement were aptly summarized in 1906 by the words of Dr. W. H. Curtis, who wrote, "The weight of evidence seems to establish the fact that old is never physiological, but pathological, at least its visible and appreciable evidences are pathological ones."<sup>1</sup> The desire for eternal youthfulness has existed since ancient times. Modern day promises of an ageless society free from the disability, pain, suffering and sorrow of old age are proof that the antiaging movement rages on. Although one can instantly see the flaws and even potential harm in such a notion, examination of antiaging movements throughout our history can provide

evidence of considerable scientific discovery. In fact, it is in the pursuit of prolonged or eternal youth that endocrinology has its birth, inextricably linking this field to antiaging medicine forever.

The concept of androgen replacement therapy began in the late 19th and early 20th centuries with the pioneering work of a few talented individuals driven to reverse the aging process and restore the vitality of youth. While the primary goal was to eradicate the disease of aging, a secondary impetus existed to eliminate the economic challenges inherent to an aging population. Many of the contributions were put forth in the name of science. However, the movement was also forced to contend with the abuse of those with questionable ethical motivation and primarily entrepreneurial intent. An academic exploration of the history of antiaging remedies and hormone replacement therapy not only emphasizes the discovery but also uncovers the pitfalls of scientific research. Plastic surgery, testosterone replacement and growth hormone injection are arguably similar pursuits, and this review underscores the necessity for critical outcomes analysis in medical research to avoid repeating the mistakes of the past.

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FIG. 1. Sketch depicting Juan Ponce de León (1460–1521) searching for fountain of youth.

## THE FOUNTAIN OF YOUTH

The story of Ponce de León searching for the fountain of youth began in the 1560s. Juan Ponce de León (1460–1521) was a Spanish conquistador who accompanied Christopher Columbus on his second voyage to the New World, and is regarded as the first European known to have set foot in Florida in 1513. As the story goes Ponce de León was searching for gold, slaves and lands to claim and govern for Spain when he overheard an Indian slave say, “In Bimini, no one grows old.” Intrigued by the idea of an ageless existence, Ponce de León embarked on the search to find Bimini and the fountain of youth (fig. 1). Although Ponce de León never found the fountain of youth, this historical narrative underscores the timeless nature of the search for longevity.

Antiaging remedies have existed since ancient times. In the late 1800s Elie Metchnikoff proposed his cellular theory of aging in which phagocytes were responsible for poisoning the body.<sup>2</sup> To oppose this process he advocated a diet rich in lactic acid believed to eradicate the body of intestinal putrefaction and decay. Charles A. Stephens used similar reasoning to argue that longevity could be found in the perfection of cell nutrition. While Metchnikoff and Stephens concentrated on nutrition and hygiene, others believed the secret to eternal youth was to be discovered within the endocrine system. This search for the fountain of youth is where modern androgen replacement therapy has its beginnings.<sup>3</sup>

## BIRTH OF ENDOCRINOLOGY AND ELIXIR OF LIFE

The notion that behavioral and sexual characteristics were linked to internally secreted substances can perhaps be first attributed to Arnold Berthold (1801–1863).<sup>4</sup> Professor Berthold demonstrated through a series of experiments the androgen dependent nature of male secondary sexual characteristics. He observed in roosters that castration led to atrophy of the comb, and disappearance in the interest in mating and aggressive male behavior. Perhaps more importantly for the purposes of this discussion, Berthold found

that these castration induced changes could be reversed by returning the testes of the castrated roosters to the abdominal cavity.

The latter part of the 19th century brought continued interest in the physiology of hormone secretion and its potential role in reversing the aging process. The notion arose that the replacement of internally secreted substances could combat the decline in the mental and physical powers brought on by old age. The French physiologist Charles Edouard Brown-Sequard (1817–1894), well-known for his contributions to neurology, is considered by many to be one of the founders of modern endocrinology (fig. 2).<sup>5</sup> Although he conducted experiments with a number of endocrine organs, he is perhaps most noted, or rather notorious, for his work on the testis. In June 1889 at the Société de Biologie in Paris, Brown-Sequard presented the results of a radical self-experiment. Believing that age had robbed him of his mental and physical faculties, he commenced with a series of 10 subcutaneous injections of an aqueous extract made from the crushed testicles of young dogs and guinea pigs. He hypothesized that these testicular extracts might be able to restore the vitality and physical attributes of youth. The purported benefits of this injection therapy included heightened intellectual capacity and sexual potency, as well as



FIG. 2. Charles Edouard Brown-Sequard (1817–1894). (Courtesy of the National Library of Medicine).

**SEQUARINE**

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The perfection of the Sequarine Serum (which embodies the very essence of animal energy) in a form for everyday use, places animal therapy far in advance of other branches of medical science. This Serum is being used with astonishing success in treating:—

Nervousness, Neurasthenia, Anemia, Rheumatism, Gout, Sciatica,	Kidney Disease, Diabetes, Dropsy, Dyspepsia, Liver Complaints, Indigestion,	Paralysis, Locomotor Ataxy, General Weakness, Influenza, Pulmonary Troubles.
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**A Remarkable Book.**

Sequarine is prepared under the supervision of J. H. Goize, M.D., the collaborator of Prof. Brown-Sequard. A remarkable book has been prepared, giving the details of its discovery, nature, and action, and copies are being presented free to the public. No sufferer, Physician, Medical Student, or Nurse should be without the Sequarine Book. To obtain it simply send name and address to C. RITTER & Co., 59, New Oxford Street, London, W.C.

FIG. 8.3. Advertisement published in *The Strand Magazine* in 1912, indicating the extravagant

FIG. 3. Advertisement depicting Brown-Sequard type elixir of life called Sequarine. Originally published in *Strand Magazine* in 1912.

significant improvement in the urinary stream and the power of defecation. Brown-Sequard is quoted as stating, “the injections have taken 30 years off my life,” and he was 72 years at the time. The results of this famous self-experiment were subsequently published in the July 20, 1889 issue of *The Lancet*.<sup>6</sup> As a result of considerable attention from the scientific community and the popular press, Brown-Sequard’s testicular extracts were later produced and marketed under the name Sequarine or Spermine (fig. 3).

The modern science of endocrinology has demonstrated that testosterone is released into the bloodstream shortly after synthesis and that little remains in the testis. Therefore, we are left to conclude that what Brown-Sequard observed was the result of a powerful placebo effect, and underscores the danger inherent in the absence of a control group.<sup>7</sup> Despite the flaws in design Brown-Sequard’s experiment quickly led to widespread interest in organotherapy, the treatment of disease with animal endocrine organs or extracts, within the scientific community and the popular press. Many believe this spurred George Murray’s monumental discovery of thyroid extract for the treatment of myxedema and, hence, the birth of modern endocrinology.<sup>5</sup>

These early experiments by Brown-Sequard lent credence to the notion that rejuvenation could be achieved through the replacement of internally secreted substances. Although Brown-Sequard’s injection therapy appeared to be successful, the doctor hypothesized that the nature of the delivery system was responsible for the limited 4-weeklong effect. The temporary nature of this effect led to the search for longer lasting rejuvenation treatments.

#### AUTOPLASTIC REJUVENATION

Eugen Steinach (1861–1944), a Viennese physiologist, had performed a number of animal experiments in the latter part of the 19th century that helped to differentiate the reproductive function of the testes from the hormonal function (fig. 4). In doing so he observed rejuvenation in older animals that had undergone vasoligation (fig. 5). These observations led Steinach to develop his theory on the autoplasmic treatment of aging.<sup>8</sup> He postulated that surgical li-

gation of the seminal ducts might induce proliferation of the hormone secreting cells of the testis. In 1918 Steinach performed the first human vasoligation procedure with the help of urologist Robert Lichtenstern. The Steinach operation claimed to restore youth and vitality and, consequently, enjoyed considerable popularity during the next 2 decades. Evidence of this can be found in the February 9, 1922 New York Times headline, “Dr. Steinach coming to make old young.” Although Steinach never made it to America, his vasoligation technique was adopted by a number of physicians such as Harry Benjamin of New York who shared a 24-year correspondence with Steinach after visiting him in 1920.

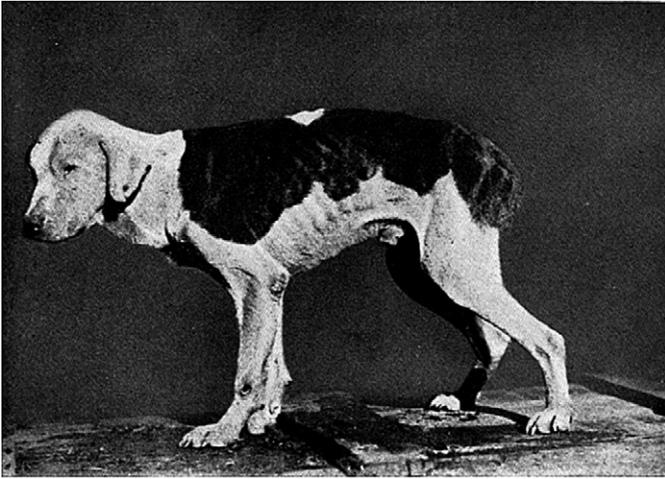
The widespread popularity of the Steinach operation is further affirmed by the celebrity clientele such as Sigmund Freud (1856–1939) and the Nobel prize winning poet William Butler Yeats (1865–1939). At least in the case of Yeats, the operation was reported to have been a success in that it revived his creative power to allow for a number of late poems recognized to be among his best work. Yeats referred to this as “a strange second puberty.”<sup>9</sup> Given the simplicity of the operation and the sensationalist nature of the media, it is not difficult to imagine how the Steinach method gained popularity, although it is certain rejuvenation was not successful in every instance. Some supporters even went so far as to argue that the Steinach operation could solve the post-WWI destitution of central Europe following the death of a significant portion of the young male population by revitalizing its older population.<sup>10</sup> Perhaps Steinach’s philosophy is stated best in his own words, “It has frequently been said that a man is as old as his blood vessels. One may have greater justification for saying that a man is as old as his endocrine glands.”<sup>8</sup>

#### SEX GLAND TRANSPLANTATION

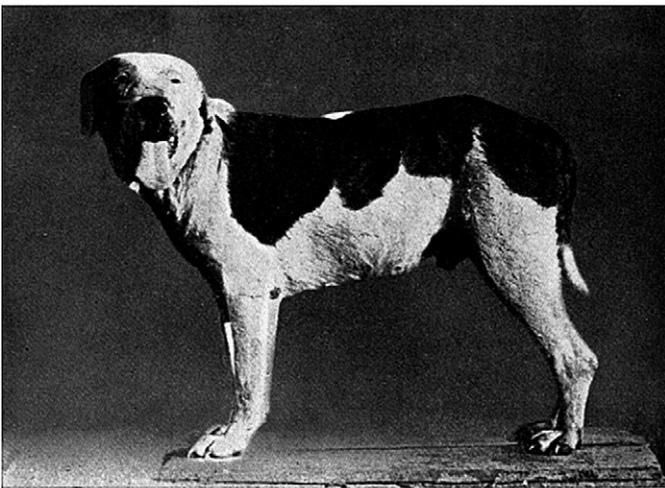
The interest in sex gland transplantation developed parallel to Steinach’s work. A pioneer of this movement was Russian born Serge Voronoff (1866–1951) (fig. 6). He left Russia when he was 18 years old to study medicine in Paris. As a young doctor he traveled to Egypt where he observed signs of



FIG. 4. Eugen Steinach (1861–1944)



Eighteen-year-old dog, before vasoligature (Wilhelm).



The same dog, after vasoligature (Wilhelm).

FIG. 5. Photographs of 18-year-old dog before and after the Steinach vasoligation operation.<sup>8</sup>

premature aging in eunuchs. This led to a series of animal experiments involving testicular gland transplantation. Voronoff reported the restoration of lost vigor in older animals that had undergone the transplantation of testicular tissue from younger animals. On June 12, 1920 Voronoff performed the first official transplantation of testicular tissue from a chimpanzee to a human.<sup>11</sup> Of course this was not as we think of transplantation today, rather the operation entailed sectioning of the monkey testis into 2 slices approximately 2 cm in size. These tissue grafts were placed within the scrotum of the male patient and affixed with sutures for 8 days. For Voronoff one of the major benefits of glandular transplantation was the ability for ongoing production of the hormone rather than the repeated injections necessary with traditional organotherapy. Voronoff reported that hormonal secretion lasted 1 to 2 years and then slowly decreased secondary to fibrosis of the grafted tissue. Voronoff's book *The Study of Old Age and My Method of Rejuvenation*,

published in 1926, provides an explanation for the development of his theory on the endocrine function of the testis and its influence on the aging process.<sup>12</sup>

This form of glandular xenotransplantation became immensely popular. Initially the operation was limited to men of means as evidenced by the reference to Voronoff as "the famous doctor who inserts monkey glands into millionaires." However, by the 1930s monkey gland transplantation was being practiced in several countries including the United States, Italy, Chile, India, Russia and Brazil. In addition to testis tissue Voronoff transplanted ovaries from female monkeys into women for the treatment of menopause. Perhaps the best evidence for the popularity of monkey gland transplantation is the necessity of the French government to ban monkey hunting in the French colonies. Even Voronoff, amazed by his success, was concerned about the supply of monkeys for transplantation. He proposed the construction of monkey houses in French Guinea to provide a continual supply of testicular tissue.<sup>13</sup> By his death in 1951 Voronoff reportedly transplanted ape tissues to 2,000 human patients. Voronoff gained international recognition for his monkey gland transplantation but he was not without critics. He was ultimately forced to end his transplantation efforts due to pressure from the scientific community, skeptical of his results.

While Voronoff's youthful rejuvenation through monkey gland transplantation campaign waged on in Europe, transplantation efforts were also under way in the United States. In fact, testicular transplantation using human testis was performed as early as 1911. Among the early endocrine pioneers were Victor D. Lespinasse (1878–1946) and G. Frank Lydston (1858–1923).<sup>14,15</sup> Testicular transplants were often advocated for more than just restoration of vigor. In an article published in the *Journal of the American Medical Association* in 1916, Lydston reported on the beneficial results of sex gland implantation for a range of medical conditions including dementia, hypertension, psoriasis, ec-

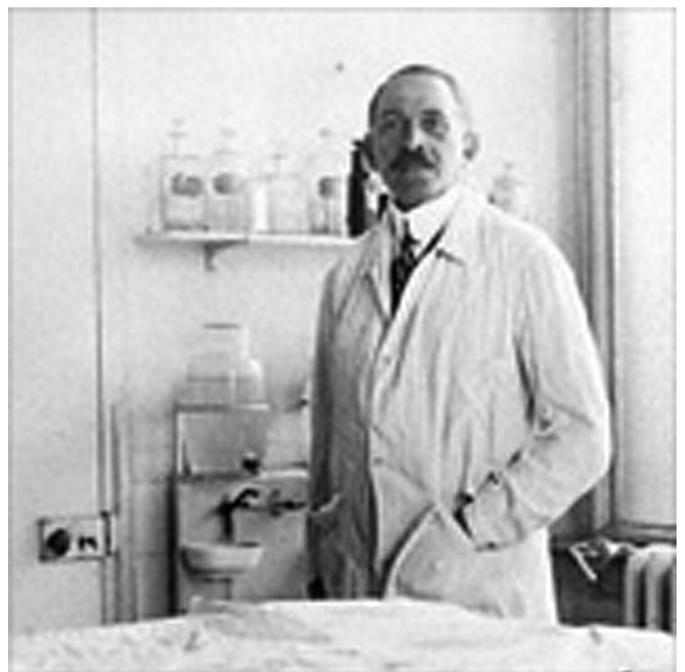


FIG. 6. Serge Voronoff (1866–1951)

zema, psychosis and cryptorchidism.<sup>16</sup> Lydston's unwavering support of the operation was clearly demonstrated when he personally underwent human testis implantation. Unlike Voronoff, Lydston allegedly implanted the entire testis, but none were orthotopic with a vascular anastomosis, rather the testes were fixed upon the abdominal wall. To perform these sex gland transplants, testes were removed from persons who had committed suicide or were executed criminals.

In the case of Leo L. Stanley (1886–1976), the unfortunate prisoners were both donors and recipients. Stanley served as the staff physician at San Quentin Prison in California, where he performed a large number of testicular tissue grafts. His results of 1,000 testicular substance implants were published in the journal *Endocrinology* in 1922.<sup>17</sup> Similar to Lydston, Stanley reported promising results for a wide variety of conditions such as diabetes, tuberculosis, epilepsy and rheumatism.

Unfortunately the sex gland transplantation movement was tainted by those with more than scientific interest. Perhaps the most colorful among these is Dr. John R. Brinkley (1885–1942), who attended Bennet Medical College in Chicago but never graduated. He bought a diploma from Kansas City Eclectic Medical University in 1915 and by 1917 had established a medical practice in Milford, Kansas. Brinkley recognized early the fortune to be made in antiaging therapies. With Chicago con man James Crawford he created a company known as Electro Medical Doctors. Under this name the pair injected colored distilled water promised to rejuvenate for \$25 a shot. Inspired by the work of Brown-Sequard, Steinach, Voronoff and others, Brinkley also began to experiment with gland transplants. His interest was certainly in large measure driven by entrepreneurial desire. The Brinkley operation to improve sexual function consisted of testicular gland transplants from goats (fig. 7). Testimonials from satisfied customers such as H. Chandler, the owner of the Los Angeles Times, led to considerable publicity for Brinkley. In addition, he started up the radio station KFKB where he lectured on his rejuvenation therapies. The Milford Messiah, as he was sometimes called, was said to have performed more than 16,000 transplants. With his rise to fame came increased scrutiny from the medical commu-



FIG. 7. Illustration summarizing life of John R. Brinkley (1885–1942). Originally printed in *New York Evening Journal*.

nity. The American Medical Association ultimately revoked his license on the grounds of immorality and unprofessional conduct. In 1930, in an effort to regain public favor and his license, he organized a massive write-in campaign to become governor of Kansas. The race was close but Brinkley ultimately lost to H. Woodring. Following 2 more unsuccessful attempts for governor he moved his family to Del Rio, Texas where he operated a radio station from Mexico, speculated in oil and studied for the Methodist ministry. Although wealthy during the 1930s, income tax problems left him bankrupt upon his death in 1942.<sup>18,19</sup>

## PAST, PRESENT AND FUTURE

The 19th and early 20th centuries were certainly notable for a renewed interest in antiaging remedies. What can be learned from this examination of the efforts of the past? Modern urology is still struggling to decide whether the decrease in male androgen levels with aging represents pathology or physiology. Although the search for the glandular fountain of youth ultimately led to the discovery of testosterone, examination of the lives and paths to discovery for these early pioneers underscores the necessity for critical outcomes analysis and stringent scientific method in the study of male sexual dysfunction, andropause and hormone replacement therapy. As the pursuit of an ageless society marches forward in full force, let us greet it with deserved skepticism to avoid letting the sins of the past haunt us.

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