

## Perspectives Article

# Regaining Lost Youth: The Controversial and Colorful Beginnings of Hormone Replacement Therapy in Aging

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The quest for regaining lost youth seems to have existed since the beginning of recorded history and has taken many forms. One strategy that began in earnest in the latter part of the 19th century and continues to have enormous momentum today is based on the notion that by replacing internally secreted substances, that is, hormones, that decline with age, the vitality and physical attributes associated with youth can be regained. Although the approach remains highly controversial as, for example, in “anti-aging medicine,” it is no more controversial than it was many years ago when the work of three high profile investigators, Charles Eduard Brown-Séquard, Eugen Steinach, and Serge Voronoff set the basis for using this strategy. In the case of all three individuals, the therapies they developed received widespread attention (including ridicule) in the popular press, were spread rapidly by practitioners of questionable training and ethical motivation, and finally and relatively quickly disappeared from common use. However, and ultimately more importantly, in the process of developing and promoting their therapies, these individuals made important contributions to the origins of endocrinology, the biology of sex, and establishment of hormone replacement therapy. It remains to be seen whether contemporary efforts using hormone replacement therapy to blunt and reverse aging have the same fate as their predecessors and make comparable important contributions to biology and medicine.

THE glamorous and youthful-looking Madame Zattiany smiled at the other middle-aged women at the luncheon. She explained how, after the First World War, when she was not quite 60 years old but already worn out in mind and body, she had gone to live in Vienna. While there, she heard of a treatment that might relieve her exhaustion and restore her youth. The essence of the treatment was stimulation of the endocrine glands, glands that, she explained, had become exhausted as a consequence of aging. In Madame Zattiany’s case, the treatment involved exposing her ovaries to X-rays, in a process that she described as painless and leaving no scar. “Almost suddenly at the end of the fourth or fifth week, it seemed to me that an actual physical weight that had depressed my brain had been lifted, and I experienced a decided activity of mind and body, foreign to both for many years. Nevertheless, the complete reenergizing of both was very slow, the rejuvenation of appearance slower still.” However, “the time came when I knew that youth was returning to my body. The treatment induces flesh, . . . my skin grew taut and lines disappear. My hair is a shade that never turns gray.”

Gertrude Atherton wrote these words in her book *Black Oxen*, which was published in 1923 (1) and made into a well-reviewed silent movie of the same name in 1924 (2). Ms. Atherton had herself received X-ray treatment and was so enthusiastic about the result that, on a trip to Germany, she proposed it as a means of allowing the country’s older

“supermen” to be rejuvenated. Members of the German Parliament ridiculed her idea as absurd (who, for example, would decide which individuals would be restored and what if those chosen did not want the procedure?) and not possible to implement (3).

The treatment described by Ms. Atherton was the women’s version of a method originally developed for men by Eugene Steinach, a Professor of Physiology at the University of Vienna. The method was intended to reactivate or stimulate the senescent “pubertal gland” located within the ovaries or testes of aging individuals. The pubertal gland was recognized as the source of secreted substances (hormones) important in determining sex organ development and secondary sexual characteristics in early life, and maintaining vigor and health in old age. In the ovary, the secretion presumably takes place in the granulosa of the follicle; in the testis, it is the interstitial cells of Leydig that would produce, at least in principle, the active agent. In the Steinach method, the testes are not irradiated, rather the interstitial, “pubertal” (Leydig? Sertoli?) cells are presumably stimulated (activated) by performing a ligation of the vas deferens. Following ligation, the spermatogenic cells atrophy and a hypertrophy of remaining interstitial cells occurs. It is the hypertrophy of the latter that results, so it was believed, in increased secretory activity, and the positive physical and functional changes experienced by many of the patients (4–6). Figure 1 shows the marked

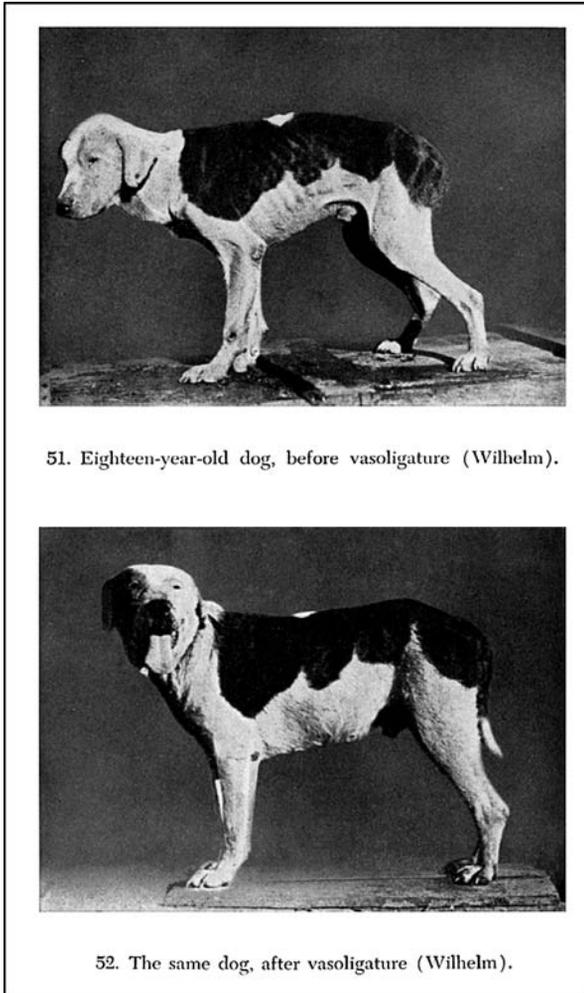


Figure 1. Before and after photographs taken of an 18-year-old dog subjected to the Steinach vasoligation technique. Note the healthier and more youthful appearance of the “Steinached” animal. [From Steinach’s *Sex and Life: Forty Years of Biological and Medical Experiments*, Viking Press, New York, 1940.]

change in appearance of an old dog subjected to the Steinach method. As noted above, Gertrude Atherton was among the most famous of these satisfied patients. The poet William Butler Yeats was another. A less satisfied subject was Sigmund Freud, who hoped that having Steinach surgery would reduce the likelihood of recurrence of the oral cancer for which he had been treated (7).

Even in its heyday, the Steinach technique (individuals who had the surgery were sometimes described as having been “Steinached”) was controversial and the findings disputed. Critics considered that whatever positive changes were observed in “Steinached” patients were the result of “auto-suggestion” (essentially the placebo effect) and, at best, short lived (6). Consequently, and within a relatively few years, the technique disappeared from use as a means of rejuvenation. It is important to note, however, that Steinach himself was, on the whole, a very careful scientist who made major contributions in understanding sex determination and sex organ development, and formulated, with Magnus

Hirshfeld, an early theory on the biological (hormonal) basis of homosexuality (8). [One of his proposed “therapies” for the latter, quickly discredited, involved transplantation of a testicle from a heterosexual donor into a homosexual, unilaterally enucleated recipient.] Steinach did not think of his ligation technique in terms of rejuvenation. Rather, he evidently preferred words like “restitution” or “reactivation” and thought of his method as a means of retarding senility, not restoring youth. In any case, the development of the Steinach technique, the publicity and notoriety it received (9), and the rationale on which it was based constitute an important part of the history of hormone replacement therapy (HRT), particularly as applied to gonadal hormones. The technique not only provided additional, albeit indirect, evidence that the gonads were the source of powerful secretory substances that passed into circulation, but also suggested that increasing the level of these substances (i.e., hormones) could have important biological and therapeutic effects in individuals deficient in these substances.

The findings of Steinach followed in the footsteps of other related but earlier research that also clearly indicated that the gonads served as endocrine organs in sex determination and, perhaps with involution, the aging process. Likely the earliest of these complementary, precedent setting approaches was an organ transplantation experiment by John Hunter (1762), which showed that testes could be successfully transferred from a rooster into a hen. [The results of this experiment were not reported directly but are mentioned in Hunter’s lectures (10)]. About a century later (1849), A. A. Berthold did a similar but much more comprehensive set of testicular transplants. In this case, however, the results of the experiments were described in detail and showed that testes transplanted into castrated male chickens (capons) restored the appearance of secondary sexual characteristics (wattles and sex combs) in the recipients and a behavior characteristic of roosters (10,11). This work not only firmly documented the feasibility of transplanting testis but also clearly indicated, since neural connections had been severed, that these organs secreted substances capable of dramatically effecting tissues in other parts of the animal’s body (10).

It was evidently a common belief in the mid-to-latter part of the 19th century that eunuchs (castrated men) and “men prone to sexual excess or masturbation” had impaired intellectual and physical activity. The eminent French physiologist, Charles Eduoard Brown-Séguard, saw these purported changes as reminiscent of the consequences of aging and therefore associated with the diminished or exhausted action of the spermatid glands (12). This idea, likely coupled with his earlier experience doing testicular transplants, led Brown-Séguard to pursue a “replacement strategy” in which an aqueous extract of dog and guinea pig testes, testicular blood, and seminal fluid was prepared, filtered, and then, in the first experiment, injected subcutaneously into his *own* arm. At the time, Brown-Séguard was 72 years old and had over the prior decade experienced losses in strength, increasing fatigue, and insomnia. In particular, he had carefully and quantitatively documented the diminishing loss of power in his forearm flexor muscles. However, after a 3-week course of injections, Brown-Séguard

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

Figure 2. An advertisement promoting the remarkable benefits following the use of a Brown-Séquard type elixir called “Sequarine.” This ad, which was first published in the *Strand Magazine* in 1912, was reproduced in Aminoff’s biography of Brown-Séquard (11).

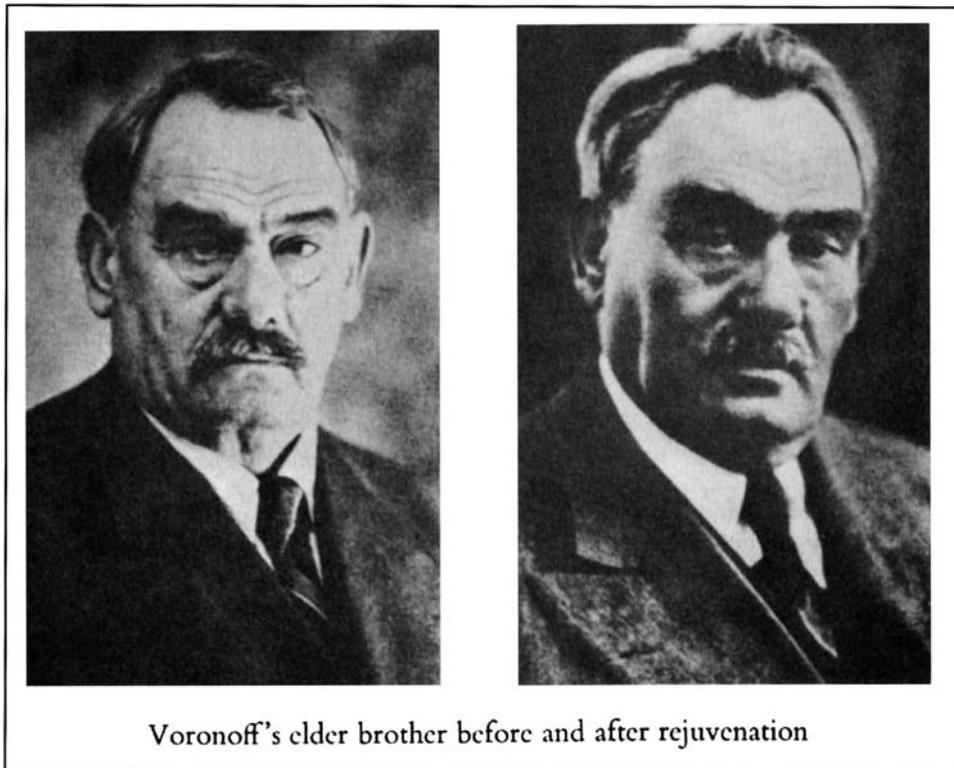


Figure 3. A more youthful appearing George Voronoff, Serge Voronoff’s older brother, following the transplantation of primate testicular tissue. The photo on the left was taken when the graft recipient was age 65. The photo on the right shows him at age 69. [From Serge Voronoff’s *The Sources of Life*, Bruce Humphries, Inc., Boston, 1943.]

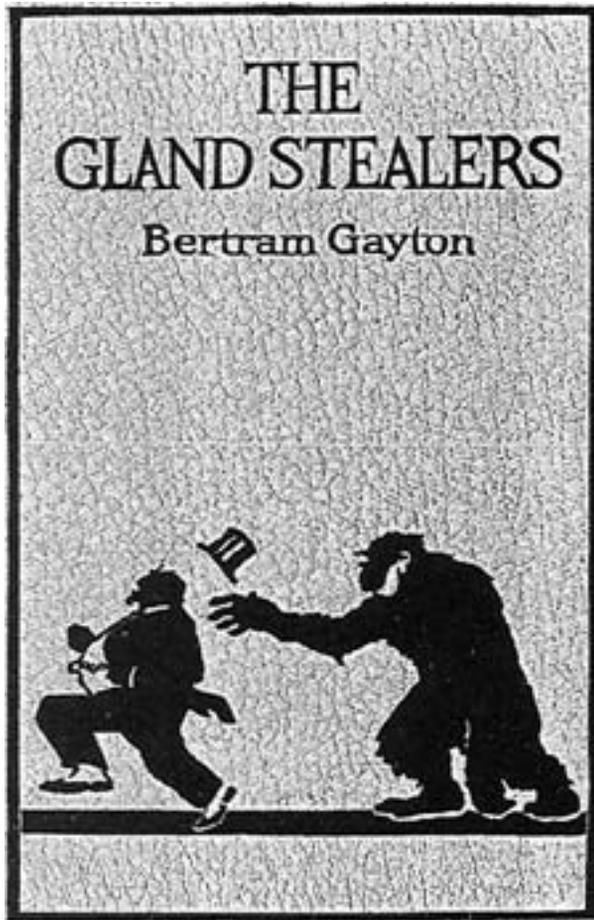


Figure 4. The cover of a book published in 1922 satirizing Voronoff's quest for primate testes for use in transplantation surgery. [Bertram Gayton, *The Gland Stealers*, J. B. Lippincott Co., Philadelphia.]

reported increased mental concentration and stamina, a marked increase in forearm strength (6–7 kg), and a substantially improved “jet” of fluid when urinating (13)!

Needless to say, Brown-Séquard's findings proved as controversial and hotly debated as Steinach's pubertal gland (vas deferens ligation) technique, even though Brown-Séquard, like Steinach, was cautious in stating his findings and actively sought confirmation of his results by other investigators (10). Indeed, in the aftermath of his announcement, it was reported that extracts similar to Brown-Séquard's had been administered by more than 12,000 physicians, probably a reflection of the “cottage” industry that quickly developed offering the Brown-Séquard elixir (most of dubious quality) to the general public (Figure 2, “Sequarine”). Indeed, in an effort to combat these unscrupulous activities, Brown-Séquard and his assistant, D'Arsonval, prepared extracts to their own specifications and distributed it *gratis* to physicians willing to test and report the potency and effect of this preparation on their patients. However, in the final analysis, confirmation of the restorative properties of the extract was not forthcoming (likely in part because the probable active component,

testosterone, dissolves poorly in water) although some physicians reported positive results.

Perhaps the most colorful and controversial of these pioneers in hormone replacement therapy and rejuvenation (and evidently a rival of Steinach) was a Russian émigré to France, Serge Voronoff. Voronoff, a surgeon, had performed a number of testicular tissue transplants in old livestock (horses and sheep), reporting that recipient animals regained the physical characteristics of younger animals including sex drive and potency (10,14). These apparently successful efforts formed the basis of Voronoff's most notorious work, *viz.*, the grafting of testicular tissue from monkeys and chimpanzees into men. Figure 3, for example, shows the change in Voronoff's brother posttransplantation surgery. Not surprisingly, this work received widespread, rather extraordinary coverage in the popular press (including cartoons of Voronoff and his monkeys). It put Voronoff at odds with many individuals in the medical community [who vocally and in writing disputed his findings, e.g., the headline in the *New York Times*, which read “Voronoff Hooted by French Doctors” (15)] and raised the ire of antivivisectionists, especially in England (14). Voronoff was also targeted in the popular fiction of the day. In one book, a satirical novel called *The Gland Stealers*, a group of wealthy elderly men go to Africa to capture 100 gorillas and take their “glands” (testicles) for transplantation (Figure 4) (16).

Voronoff was not the only physician of his generation who practiced testicular tissue grafting. Some of these contemporaries were clearly serious in their intent to do good by their efforts; others had motives that were more problematic and questionable. For example, on the positive side, Dr. L. L. Stanley was a staff physician and surgeon at San Quentin Prison in California who performed testicular tissue grafts from a variety of animal donors on 656 subjects including inmates, almost 100 unconfined individuals, 13 physicians, and 7 women. His findings [reported in the *Journal of Endocrinology* in 1922 (17)] indicated that the tissue grafting technique was successful in treating a wide range of disorders including general asthenia (weakness, loss of weight, sleeplessness), rheumatism, poor vision, and acne vulgaris (Figure 5). In later years, Stanley distanced himself from this earlier work. On the other side of the spectrum was “Dr.” John Brinkley, a radio evangelist who combined testicular grafts from goats into men (he was identified as the “goat gland doctor”) with preaching the Christian gospel (Figure 6). [In Milford, Kansas, he made an effort to found the Brinkley Methodist Church.] His career as a rejuvenator/healer and radio broadcaster (and politician) lasted from the early 1920s into the late 1930s, when he was forced into bankruptcy (18,19). [Additional details on the testicular transplantation techniques practiced by Voronoff, Stanley, and Brinkley are provided in the Appendix at the end of this article.]

From a contemporary perspective, the efforts of Brown-Séquard, Steinach, and Voronoff probably seem naïve, unethical by some standards, and potentially dangerous to the patient. However, at least at a superficial level, the approaches were logically developed and consistent with the knowledge available at the time. Moreover, the work of these

ANALYSIS OF CASES			
	TOTAL CASES	BENEFITED	NOT BENEFITED
General asthenia.....	330	305	31
Rheumatism.....	58	49	9
Acne vulgaris.....	66	54	12
Neurasthenia.....	56	33	23
Poor vision.....	41	32	9
Asthma.....	21	18	3
Tuberculosis.....	17	10	7
Senility.....	34	27	7
Sex lassitude.....	95	81	14
Impotence.....	19	12	7
Psychopathic inferiority.....	8	..	8
Epilepsy.....	5	3	2
Dementia praecox.....	8	1	7
Paranoia.....	3	2	1
Diabetes.....	4	3	1
Locomotor-ataxia.....	3	3	..
Drug addicts.....	32	..	..
Dead.....	11	..	..
Unclassified.....	28	..	..
No report.....	30		

Figure 5. Data from Stanley's paper in *Endocrinology* showing the results of testicular tissue grafts to inmates and staff of San Quentin Prison. In all, about 650 individuals received transplants, including 7 women (17).

early investigators clearly contributed to the identification of gonads as a source of hormone(s), demonstrated the role of these hormones in sex development both from an anatomical

and behavioral perspective, and set the basis for hormone replacement therapy in normative clinical medicine. In addition, these individuals made significant contributions beyond the work described here. For example, during Voronoff's career, he helped establish transplantation and graft surgery as a viable clinical strategy. Finally and fundamentally, within the context of biogerontology, the collective efforts of Brown-Séquard and colleagues provided the context for viewing aging as, at least in part, the result of hormone deficiency. Thus, if there is a natural decline with age in the level of a particular hormone, and this decline seems to be associated with senescent change, then a rational approach to reversing these changes, at least in principle, is to restore the level of hormone through replacement. This was certainly the logic behind the work of Brown-Séquard, Steinach, and Voronoff. It is also behind present-day efforts using testosterone (particularly for the frail patient), dehydroepiandrosterone (DHEA), and growth hormone (GH) to ameliorate, if not reverse, age-related declines in body structure and function. In fact, the latter hormone, GH, is the cornerstone of a rejuvenation therapy currently widely promoted and advertised as "anti-aging medicine," particularly on the World Wide Web; see, for example, <http://www.antiaging.com> and <http://www.worldhealth.net>

While it is not the purpose of the present review to specifically critique hormone replacement therapy as a means of attaining rejuvenation, it is instructive to look at the strong cautionary message that follows from the endeavors of Brown-Séquard and his colleagues from the late 19th and early 20th century. The work of these individuals received high levels of attention in the medical and popular press, and their methods were quickly adopted by other practitioners, including many qualified physicians. However, in a relatively few years, these approaches were



Figure 6. Illustrations and part of the text from a planted story in the *New York Evening Journal* highlighting John Brinkley's career as a goat gland transplant surgeon, rejuvenator, and Christian evangelist. [From Carson's *The Roguish World of Dr. Brinkley* (19).]

discredited and disappeared from accepted clinical practice. Will, for example, the use of GH in anti-aging medicine have the same fate? Its application follows the same logic (compensation or replacement of hormone following an age-related decline in hormone production), its purported benefits are widely promoted, and it has received heavy criticism from the established, mainstream biomedical community [e.g., (20,21)]. (A recent series of articles on the biological, ethical, and legal aspects of anti-aging is also to be found in the July 2004 issue of the *Journal of Gerontology: Biological Sciences*). For now, a very wise position for current and potential consumers of anti-aging medicine would seem to be “Buyer Beware.”

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## APPENDIX

Testicular transplant technique varied in terms of species of donor animal, manner of tissue preparation, and site of implantation. Stanley (17) used a number of different ungulates (goats, rams, and deer) as donors, Brinkley (22) employed Toggenberg goats exclusively, and Voronoff took tissue from several primate species including chimpanzees and apes (23). Stanley minced the testicular tissue and injected the particulate residue subcutaneously into the abdomens of his patients, while Brinkley inserted whole testis, freed of surrounding connective tissue, into a pouch in the scrotum. In preparing the latter site, the vas deferens of the patient was split longitudinally (to ensure patency), and, following placement of the graft, both nerve and a small artery were transplanted (relocated) to the graft area. Voronoff, whose surgical technique is described in great detail in reference 23, cut the donor testis into six longitudinal wedges and placed one to several of these under the connective tissue capsule of the recipient's testis. Voronoff emphasized the importance of abrading the host tissue site to stimulate angiogenesis as a means of facilitating the development of a host vascular supply to the graft. None of the surgeons reported significant complications as a consequence of the transplant procedure.

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