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Eugen Steinach - the First Neuroendocrinologist

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In 1936, Eugen Steinach and colleagues published a work that brought steroid biochemistry to the study of sexual behavior and, using synthetic androgens and estrogens, foreshadowed by an astonishing four decades the discovery of the central role of estrogen in the sexual behavior of male rats. We offer an English translation of that paper, accompanied by historical commentary that presents Steinach as a pioneer in reproductive neuroendocrinology. His work (1) established the interstitial cells as the main source of mammalian gonadal hormones; (2) launched the hypothesis that steroid hormones act on the brain to induce sexual behavior and that chronic gonadal transplants produce sexual reversals in physiology and behavior; (3) demonstrated the influence of sensory stimulation on testicular function; and finally, (4) spearheaded the development of synthetic commercial hormones for clinical use in humans. Though its applications were controversial, Steinach's research was confirmed by many, and his concepts were applied to fields such as oncology and vascular disease. His contemporaries lauded his research, as indicated by his seven Nobel Prize nominations. But Steinach's basic research was rarely acknowledged as the field flourished after 1950. The translation and our commentary attempt to reverse that neglect among behavioral neuroendocrinologists and clarify his central role as a founder of the neuroendocrinology of sexual behavior and reproduction.

In 1936, Eugen Steinach, Heinrich Kun, and Oskar Peczenik published a paper (1) describing the role of estrogen in androgen-activated sexual behavior in male rats. That role of estrogen was rediscovered 36 years later by investigators who were unaware of Steinach et al´s paper (2–4). His seminal discovery remained unnoticed as reproductive and behavioral endocrinology flourished in the 1950s, and it was found only recently (5). By contrast, in Steinach's time its significance was immediately recognized by biochemists (6–8), oncologists (9), circulatory physiologist (10, 11), and by the Nobel Prize Committee (12), Steinach was nominated for the Nobel Prize seven times. The international acclaim afforded Steinach did not extend to the United States where physiological and behavioral research was, like the country as a whole, provincial and isolationist. Only Frank Beach (13) acknowledged the significance of Steinach´s work:

"Steinach´s animal experiments were carefully conducted and his theoretical concepts were highly original some of them so much so that their final test was delayed for half a century until necessary technical advances had taken place."

We offer here an English translation of the paper announcing this finding accompanied by our historical commentary, which presents Steinach as a pioneer in reproductive neuroendocrinology. Though his work was sometimes controversial, well before the chemical structures of steroid hormones had been uncovered, Steinach used chronic same-sex, cross-sex, and dual-sex gonadal transplants in mammals to explore the action of the putative hormones on the development and maintenance of sexual anatomy, gonadal physiology, and sexual behavior. We summarize these accomplishments as the scientific foundation of the discovery of estrogen's role in male

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Abbreviations:

mammals. By publishing the translation of Steinach et al´s paper (1), Endocrinology takes a major step in recognizing a pioneer in the history of endocrinology.

Biographic Sketches

Eugen Steinach was born in 1861 to prominent Jewish parents in the city of Hohenems, in the Austrian province of Vorarlberg. Both his grandfather and father were physicians - his father a student of Ernst von Brücke, who advocated a physiology based solely on physico-chemical processes. After studying in Geneva, Vienna, and Innsbruck, Steinach became assistant to Ewald Hering at the German University in Prague, where he directed one of the first comparative physiology institutes. In 1912, he was appointed head of the Department of Physiology at the Institute for Experimental Biology of the Imperial Academy of Science, the so-called Vivarium. Steinach was well known in Vienna; Karl Kraus mentioned him in "Die Fackel", with his wife Antonia (nee Thumim) he was acquainted with Arthur Schnitzler, and they were guests at the influential Salon of Bertha Zuckerkandl. They even interacted with Sigmund Freud, although probably skeptically, as a Freudian analysis of homosexuality elicited the response: "Freud ist ein Trottel" (Freud is a Meshugana) from one of the participants (14). In 1922, the Austrian Federal Film Agency supported the production of "The Steinach Film" a documentary on Steinach´s research and the first sex education film. When the Nazis seized power in Austria in March 1938, Steinach and his wife, who was also of Jewish descent, were on a lecture tour in Switzerland. The new regime destroyed Steinach´s library and his research material and prevented him and his wife from returning to Vienna. Steinach´s wife committed suicide in Zurich in September 1938, and Steinach died lonely and disillusioned near Montreux in May 1944 (14, 15).

Heinrich Kun, also of Jewish decent, was born in 1906, received his PhD with Steinach in 1931, and participated in some of the pioneering discoveries including the 1936 paper. Sadly, Kun fared even worse than Steinach, after the Nazi take over he was deported to an unknown concentration camp in Yugoslavia and his fate is not known, but presumably he died there (16).

Oskar Peczenik, born in 1898 and a student of Alois Kreidl in the Department of General and Comparative Physiology of the University of Vienna, became a member of Steinach´s group in 1935. He was also forced to emigrate, working in the Department of Zoology at the University of Glasgow and in the Research Department at the Boots Pure Drug Co. Ltd. in Nottingham. Peczenik went to Israel in 1954, working in the Central Laboratories of the Ministry of Health, Joha, Jerusalem, on local anesthetics, the adrenocorticotropic hormone, and the toxicology of nitrogen mustard.

These were the people. What was the science of their times?

Prevailing Concepts of Bisexuality

A major idea of Steinach´s is that each sex houses the potential to develop as the opposite sex: "Between a real man and a real woman there are innumerable others, some of which are significantly characterized as belonging to the 'intermediate sex'" (17). Steinach noted that the gonads of both sexes produce the hormones of the opposite sex and suggested that individual differences in physical characteristics and behavior, as exemplified by the quote, were the result of differences in endocrine balance (17).

The concept of bisexuality, which Steinach entertained, has a long history. The ancient Greeks believed that human life began as a single being created by the gods as a plaything. Concerned their creation was becoming too rambunctious and might challenge their power, Jupiter divided them using a hair, creating Halflings that would spend their lives constantly seeking their opposite so as to reunite and become whole (18). Subsequent myth and scripture regarded humans and animals as inherently bisexual such that each individual could be placed on a continuum between masculinity and femininity; that is, each individual contained the essence of maleness and femaleness, with the balance of the two properties specific to the individual. This carried over into belief systems regarding how to predetermine and diagnose the sex of offspring (19). Further, many recognized a complementarity of these states that was essential for successful reproduction and a happy family life. It is important to emphasize that the brain was thought to be inherently bisexual and philosophers emphasized the similarities between the sexes.

The realization that reproduction (union of gametes and their result) and sexuality (as sets of individual attributes and behavior) were different in origin was relatively recent, beginning in the late 1800's - early 1900's. Two Viennese psychiatrists, Richard von Krafft-Ebing and Sigmund Freud, and a Berlin otolaryngologist, Wilhelm Fliess, posited that the mechanisms controlling sexual behaviors were equally represented in 'centers' in the brain, and that a dynamic tension between these centers accounted for the degree of masculinity vs. femininity an individual exhibited (20). This view was based on the then recent discovery that during embryogenesis, the ovaries and testes developed from a common anlagen while the accessory sex structures developed from dual anlaga (21, 22). It was during this period that "bisexual" came to indicate "bipotential", meaning that the same anlagen would give rise to one of two states, rather than the same

structure housing two distinct states. According to Freud, "the conception which we gather from this long known anatomical fact is the original predisposition to bisexuality, which in the course of development has changed to monosexuality, leaving slight remnants of the stunted sex" (23).

By the early1940's it was well accepted that: (i) hormones change the individual's sensitivity to specific stimuli (eg, tactile, visual, and odor cues) and (ii) while males and females exhibit characteristic behaviors, they have the capacity to display the behavior of the opposite sex. Indeed, Frank Beach in his compendium *Hormones and Behavior* (24) devoted the second chapter ("Reversal or Bisexuality of Mating Behavior") to this common observation. Beach stressed that heterotypical behaviors were never exhibited coincidentally, but alternately and were elicited by the stimulus context, and not by specific hormones. Hence, the role of internal context (hormones) and external context (behavioral stimuli) were given equal weight. Subsequent research, particularly after 1959, tended to drop the latter in favor for the former (25).

Hormones, Development, and the Brain

Already in 1894, while still in Prague, Steinach made the pioneering observation that sexual behavior of male rats persists very long after castration (26), replicated only 30 years later (27). And as early as 1910, Steinach showed that injection of extracts of testes and of brain taken from male frogs in reproductive condition, but not those from nonreproducing males, restored sexual clasping in castrated frogs (28). Unfortunately, there is no information on how the extracts were prepared, the records may have been lost when the Nazi's destroyed Steinach's laboratory materials. These findings allowed him to challenge those who believed that the clasping reflex was controlled by nerve impulses from the gonads, arguing instead for the specific effect of chemicals produced in the testes on the brain. Interestingly, the only other control "organ juice" that showed any effect was an ovarian extract. This suggested to Steinach that female gonads produce a "relative" of the substance secreted by the testes (28).

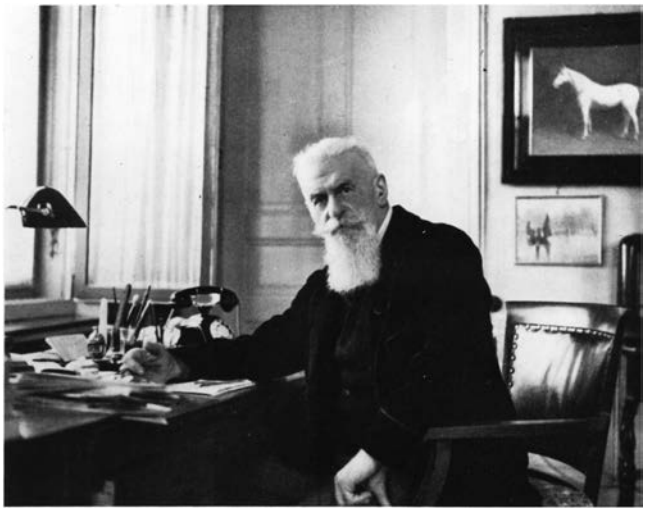

Figure 1. Eugen Steinach (1861–1944). Reproduced by permission of the Library of the New York Academy of Medicine.

In the same paper, Steinach (28) inferred that normal copulatory behavior also required the action of hormones on the developing brain. Three to six week old rats were castrated and both testes were repositioned either in their stomach musculature or pelvis. The animals showed full masculine somatic development, and as adults they behaved like intact breeding males. Steinach concluded that the development of masculinity resulted from the action of hormones on the central nervous system (CNS), enabling males to respond to signals from females. Because in frogs the behavioral effects occurred more rapidly than those affecting peripheral tissues, Steinach asserted that the first effect of the secretions was in the brain, not in peripheral tissues. He termed the process the "erotization (Erotisierung) of the CNS". Steinach's 1910 work offers perhaps the most precise early experimental evidence that hormones shape the development of brain and behavior in frogs and mammals.

The Importance of Sensory Stimulation

In the late 19th century, as Steinach began his research, the nervous system was thought to control the body. Steinach changed that paradigm by demonstrating the autonomous effect of endocrine secretions, while maintaining the concept of bisexuality (29). Although Steinach's early work falsified the established hypothesis that nerve impulses from the gonads release ready-made sexual reflexes, he worried that others might oversimplify his alternative hypothesis: that behavioral development was guided by secretions. Stressing the effect of secretions did not mean that the nervous system played no role. In part to explore neural control of the secretions, Steinach began isolation/stimulation experiments in 1924 to show that the supposed "dethroning" of the nervous system was an erroneous oversimplification. Indeed, the pattern of questions addressed by his research program (including work on the pituitary begun in 1914) shows that Steinach believed that in mammals hormones, brain, and behavior functioned in dynamic interplay with one another and with the environment.

To demonstrate this, mature male rats were raised for weeks in isolation from females. When at 4–5 months of age males were exposed for a few minutes to receptive females, all responded with strong sexual pursuit. With longer periods of isolation, however, the intensity of

males' reactions to receptive females became weaker; eventually they lost their "libidos," their prostates and seminal vesicles atrophied, and spermatogenesis ceased. Steinach then modified their cages, adding small compartments that gave the males olfactory exposure to, but no direct interaction with receptive females. Some males were even blinded to rule out visual stimulation. After two or three weeks of exposure, the barriers were raised, and the males actively pursued the females, which responded with lordosis and mating. Histological analysis of the males' gonads showed both live sperm and numerous interstitial cells filled with secretory granules. The males' normal drive states had been restored through sustained exposure to the odor of receptive females. To Steinach this meant that the nervous system played a critical role in the integrity of the sex drive. The libidoless males had undergone a "new erotization (Neuerotisierung)" (30). Steinach concluded: "The nervous, that is to say, psychic processes exercise a powerful controlling influence on the inner-secretory activity of the gonads through which bodily and psychological maturity can be automatically protected from regression or possibly from persistent depression (30)." He speculated that the mechanisms involved increases in blood flow mediated by the autonomic nervous system's effect on the gonads. He also noted the possible role of the anterior pituitary, which, in 1928, he and Kun had shown could cause similar changes in the sex drive (31).

In all of his work, Steinach repeatedly used the word "psychic" to refer to both brain and behavior. Plus, because neither the cellular origins of the chemicals nor their chemical structures were known before 1930, Steinach correlated behavioral changes with changes in gonadal cellular morphology using behavior to infer the impact of secretions on sexual development, brain, and behavior. But in the 1920s, behavior was not yet considered a reliable indicator of physiological processes. As a result some skeptical scientists disregarded or challenged his research. That work nonetheless had a pioneering effect on behavioral neuroendocrinology well before many scientists accepted behavior as bioassay of brain processes.

Transplanted Gonads, Behavioral Hermaphrodites, and the Woman Question

Steinach pioneered castration plus gonadal transplants and published extensively using this method (eg, 32–34). He completed heterologous transplants as well as crossed-sex, and dual transplants in males and in females. All procedures produced clear changes in masculine or feminine behavioral development that matched the character of the implanted gonad. Importantly, in all experiments, histological analysis of the cellular structure of the gonads showed large increases in interstitial cells coincident with the changes in behavior. And when both ovaries and testes were positioned in the stomach musculature of the same animal, male vs female behavioral attributes alternated periodically in a single animal. The alternating phases began with a variety of male behaviors and shifted to a phase of female behaviors, which lasted for 2–4 weeks. Steinach expressed surprise that the nervous system responded so markedly to the fluctuations in hormone levels and that the neurobehavioral changes recurred throughout the rest of the animals' lives. In the third edition of Arthur Biedl's ground-breaking textbook, Innere Sekretion (35), the author noted that Steinach's transplants had established a sexually specific effect of gonadal secretions on the development of masculine and feminine behavior. Steinach had created masculine females, feminine males, and, sometimes, behavioral hermaphrodites at just the time when many people resisted the great changes then occurring in Western sexual mores. His findings must have instilled the fear of social chaos in many, particularly as regards the "women question", the possibility of "physiological hermaphroditism", and nature of homosexuality. For a time the German sexual reformer Magnus Hirschfeld used Steinach´s experiments to argue for gay rights, stating in a pioneering film on the topic: "His experiments prove that sexual intermediates who seemingly differ only on a psychological level are in fact physically determined" (36).

The Interstitial Cell Question

In the 1920s, the vasoligature procedure became associated by many in the United States with Steinach's advocacy of "rejuvenation," a forerunner of hormone replacement therapy promoted in the US by the New York physician Harry Benjamin (37). But in the preceding decade Steinach's research program was devoted to what in Central Europe was called the "interstitial cell question." This was the scientific debate surrounding the function of gonadal interstitial cells, which were discovered in the testes by Franz Leydig in 1850. At issue in the early years was which tissues in the testes produced the putative hormones. Were the interstitial cells secretory cells or merely connective tissue that might absorb the metabolic products of other processes? Two camps emerged that divided physiologists who were interested in sexual function, from cellular morphologists more interested in morphogenetic tissue origins. The debates usually pitted those who argued that in males sperm were the source of the sexual chemicals (they viewed the interstitial cells as connective tissue) against those who, following the French anatomists Paul Ancel and Pol Bouin, who proposed the idea, and Steinach, who confirmed it experimentally in mammals, instead accepted the interstitial cells as secretory cells that

produced the gonadal hormones shaping sexual development.

Though the interstitial cell question was still in debate and many cytologists supported the connective tissue hypothesis, by the 1920s Steinach had become the leader of a Central European school of reproductive endocrinology advocating the interstitial cells as the source of the hormones involved in shaping masculinity and femininity in birds and mammals. His histological analyses regularly showed that the behavioral changes produced by transplants were accompanied by the proliferation of interstitial cells in the repositioned gonad (sometimes with few or no spermatozoa present). But Steinach´s science was embedded in social and medical disputes that added to the controversy surrounding his work. He was devoted to clinical application as well as basic science, and his strong advocacy of "rejuvenation", a surgical procedure that he developed to increase sex hormone secretion and thereby invigorate the elderly (37, 38), was linked to the interstitial cell question. The procedure, which was sometimes termed "being Steinached", was overly popularized in both literature and in advertisement in America, a practice that Steinach himself abhored. In addition, Hirschfeld used Steinach´s experimental and clinical evidence to argue for the decriminalization and emancipation of male homosexuality (39). At the time, much European psychiatry still characterized homosexuality as a degenerative neural disease. Hirschfeld and Steinach instead presented homosexuality as an unusual developmental state originating in normal endocrine processes, a highly controversial view.

Even in the face of controversy, however, by the mid 1920s, Steinach´s experimental conclusions on the interstitial cell question had been elaborated by several others, including Marianne Stein, Alexander Lipschütz, and Knud Sand. Some scientists nonetheless, rejected the endocrine function of the interstitial cells well into the 1930s and 40s (40). And resistance to the idea prevented Steinach from getting the Nobel Prize in 1921 (see below).

Synthetic Sex Steroids and the Contraceptive Pill

Steinach´s research on the effects of transplantation of the gonads fuelled the interest of the pharmaceutical industry in preparing ovarian and testicular steroids for clinical use. Steinach and Walter Hohlweg started developing synthetic gonadal steroids with the Schering research laboratory in Berlin in 1923, and in 1928, when Hohlweg moved to Berlin, the first oral estrogen, Progynon, was launched on the market (Figure 2, 41). In the same year, Steinach and Kun proposed pituitary-ovarian feedback (31) and simultaneously, Ludwig Haberlandt described the principles of hormonal contraception (41). These were times of rapid development; in 1932, Hohlweg and Junkman (42) demonstrated the role of the brain in the pituitary-ovarian feedback that Steinach and Kun (31) had suggested, a major step ahead in the history of neuroendocrinology (43).

Very quickly, Adolf Butenandt elucidated the structure of the first steroidal sex hormone (44), Hohlweg and Hans Herloff Inhoffen synthesized the powerful oral estrogen, ethinylestradiol (45), and subsequently, Inhoffen developed ethisterone (Proluton C), the first oral gestagen (46). By 1939, the principles contraception were understood, the structures of the decisive hormones had been analyzed, a relatively economical synthesis based on cholesterol was available, and an oral estrogen as well as a progestin preparation had been developed (47). Thus, all prerequisites for a contraceptive "pill" were fulfilled. However, the project was prevented by the Nazis, who rejected birth control.

The translated paper shows the power of these newly available synthetic sex hormones. Steinach, who had moved the field forward with pioneering mammalian transplants, also helped pioneer the methodological shift from transplants to chemical extracts and synthetic hormones. And, in the process, he discovered the role of estrogen in androgen-activated sexual behavior in male rats.

Steinach's Nobel Prize Nominations

Steinach was nominated for the Nobel Prize for Physiology or Medicine seven times between 1920 and 1938 (12) and he was a leading candidate on four occasions, competing with 12, 18, 25, and 26 other nominees, including Edgar Adrian, Walter Cannon, Otto Loewi, Ivan Pavlov, Charles Sherrington, and Otto Warburg.

Already in 1921, the nominator pointed out that Steinach had demonstrated the behavioral effects of gonadal transplantation and suggested that the interstitial cells mediate those effects. With the 1927 nomination it was noted that the role of the interstitial cells had been confirmed and that the gonads exerted sex specific and antagonistic effects, which also had been confirmed by several laboratories. Additionally, the clinical implications of the work were mentioned. In 1930, Steinach´s contribution to the development of the synthetic ovarian hormone, Progynon, was mentioned and in 1938, the nominators pointed out that Steinach´s research was so well known around the world that only a short presentation was necessary. This prompted an evaluation by Göran Liljestrand, professor of pharmacology at the Karolinska Institute and secretary of the Nobel Prize Committee for 42 years (12), longer than anyone else has served as secretary and a period over which he met quite a few prize winners. Liljestrand pointed out that Steinach had been nominated several

times, that he clearly deserved to be awarded the prize and that he barely missed it in 1921 because two members of the Nobel Committee expressed skepticism concerning the role of the interstitial cells and the clinical applications. Liljestrand outlined Steinach´s main findings. Thus, Steinach had managed to "malemake" females and "femalemake" males and "numerous replications have shown that these observations are correct." He further wrote, "it appears obvious to me" that the "lability" of sex and the existence of "*bipotentiality . . . is a fact of fundamental importance*" (italics added). In fact, Liljestrand considered the discovery of bipotentiality to be Steinach´s most important finding. Liljestrand commended Steinach for developing "a lively scientific activity" despite his advanced age, including studies of the "*sensory control of sexual behavior and the role of estradiol in potentiating the effect of androgens in the control of sexual behavior*" (italics added) Liljestrand wrote, "*addition of a minor amount of female hormone reduced the dose of male hormone that was otherwise necessary*" (italics added) and he concluded that Steinach deserved the Nobel Prize long ago, but that he was now too old (Steinach was 67) and "the value of his contribution has not undergone a substantial increase" since 1930.

Figure 2. The ad used for the launch of Progynon by Schering in 1928. Reproduced with permission of Bayer AG**.**

Concluding remarks

The birth of the new "glandular science", ie, endocrinology, instilled optimism to the extent that the hope for the solution of virtually all clinical problems was created (29). Interestingly, this hope is remarkably similar to today´s hope that the new science of "personalized medicine" will be similarly effective (eg, 48). Unsurprisingly, Steinach's advocacy of rejuvenation and his promotion of clinical treatments with synthetic hormones did not quite live up to expectations. This, however, should not subtract from the fact that Eugen Steinach made discoveries of fundamental importance in the endocrinology of reproduction, and that he is clearly a founder of the neuroendocrinology of sexual behavior. He may even be the first neuroendocrinologist.

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