Randy J. Nelson ·
Zachary M. Weil *Editors*

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Painting by Jay Rosenblatt (Chapter 13). Rosenblatt explored themes in his art that mirrored his interest in the behavioral neuroendocrinology of parenting. Image courtesy of Nina Rose

Dedicated to our families …

Foreword

Behavioral neuroendocrinology is the scientific study of the interaction between hormones and behavior. This interaction is bidirectional: hormones can affect behavior, and behavior can influence hormones. Hormones, chemical messengers released from endocrine glands, travel through the blood system to influence the nervous system to regulate the physiology and behavior of an individual. Hormones change gene expression or the rate of cellular function, and they affect behavior generally by increasing the probability that a given behavior will occur in the presence of a specific stimulus. Hormones achieve this by affecting individuals' sensory systems, integrators, and/or effectors (output systems). Because certain chemicals in the environment can mimic natural hormones, these chemicals can profoundly affect the behavior of humans and other animals. Behavior is generally thought of as involving movement, but nearly any type of output, such as color change, can be considered behavior; for example, color change among chameleons is a behavioral response. A complete description of behavior is required before researchers can address questions of its causation. All behavioral biologists study a specific version of the general question "What causes individual A to emit behavior X?" Behavioral endocrinologists are interested in the interactions between hormones and behaviors.

The study of the interaction between hormones and behavior has been remarkably interdisciplinary since its inception; methods and techniques from other scientific disciplines have been borrowed and refined to shed light on this relationship. Psychologists, endocrinologists, neuroscientists, entomologists, zoologists, geneticists, molecular and cellular biologists, anatomists, physiologists, behavioral ecologists, psychiatrists, and other behavioral biologists have all made contributions to the understanding of hormone-behavior interactions. This exciting commingling of scientific interests and approaches, with its ongoing synthesis of knowledge, has led to the emergence of behavioral neuroendocrinology as a distinct and important field of study. The scientific journal *Hormones and Behavior* began publication in April 1967, and a scientific organization devoted to the study of hormones and behavior, the Society for Behavioral Neuroendocrinology (SBN), was founded in 1996. Both the journal and scientific society are growing with membership in SBN now over 500 members. The number of Behavioral Neuroendocrinology undergraduate courses has grown from about 20 in North America in 1995 to hundreds in 2022.

Hermann Ebbinghaus stated that psychology has a short history but a long past, and the same can be said of behavioral neuroendocrinology. Although the modern era of the discipline is generally recognized to have emerged during the middle of the twentieth century with the publication of the classic book *Hormones and Behavior* by Frank A. Beach in 1948, some of the relationships among the endocrine glands, their hormone products, and behavior have been implicitly recognized for centuries. The goal of this book is to track the development of the field from the first recognized paper in the field by Arnold Berthold in 1849 (although it was mostly ignored for the ensuing 50 years) to the major contributors of the past century.

A useful starting point for understanding research in hormones and behavior is a classic nineteenth-century experiment that is now considered to be the first formal study of endocrinology (Chap. 1). This remarkable experiment conclusively demonstrated that a substance produced by the testes could travel through the bloodstream and eventually affect behavior. Professor Arnold Adolph Berthold, a Swiss-German physician and professor of physiology at the University of Göttingen, demonstrated experimentally that a product of the testes was necessary for a cockerel (an immature male chicken) to develop into a normal adult rooster and display typical rooster behaviors such as crowing and fighting.

One way in which to explore the history and development of this field is by exploring the women and men who conducted the studies that revealed these hormone-behavioral relationships. To that end we will enlist the help of the individuals who knew these pioneers best to describe their backgrounds and discuss the way in which their work has shaped the field.

Now is the perfect time for this book. The field is burgeoning and interest in the development of theoretical perspectives is thriving. Moreover, although this field was dominated by men early on, it has become a field with near sexual parity among its faculty, society membership and leadership, and thus serves as an example of equitable science, training, and advocacy. As noted in our final chapter, the same is not true for individuals from other underrepresented groups. We hope this recognition of so-called hidden gems of scientists promotes more advocacy for equitable representation of scientists within behavioral neuroendocrinology.

Individuals were selected for inclusion based on several criteria. First, we made a list of individuals who have made significant contributions. Second, we limited inclusion to only individuals who had retired or passed away. Third, we circulated the list among the contributors and invited them to add additional names that we may have overlooked. Obviously, this involves a series of judgment calls that are informed by our own biases and experience, and we apologize in advance for any omissions. We hope you enjoy reading this volume as much as we did compiling it.

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15 March 2022 Zachary M. Weil

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Arnold Adolph Berthold

1

Zachary M. Weil and Randy J. Nelson

Abstract

Arnold Adolph Berthold was a German physician-scientist and textbook author who is most recognized as the author of the first published experiment in endocrinology. This study reports several morphological and behavioral outcomes of an endocrine manipulation that involved castration and reimplantation of rooster testes. His insightful experiment conclusively demonstrated that a substance produced by the testes could travel through the bloodstream and affect morphology and behavior and set the stage for understanding how blood-borne products could affect brain and behavior.

Keywords

Endocrinology · Rooster · Testes · Castration · Male behavior

One goal of this volume is to track the development of the field of Behavioral Neuroendocrinology by highlighting major contributors to the field. We start here with Arnold Adolph Berthold (Fig. 1.1), the recognized author of the first published experiment in endocrinology that reports several behavioral outcomes of an endocrine manipulation (Berthold, 1849, Translation by Quiring, 1944). His remarkable experiment conclusively demonstrated that a substance produced by the testes could travel through the bloodstream and eventually affect behavior.

Berthold was born in 1803 in the small Westphalian town of Soest near Münster. His early life was roiled by the political instability surrounding the Napoleonic

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Fig. 1.1 Arnold Adolf Berthold. (Courtesy of the National Library of Medicine)

wars, and his birthplace was variously part of an independent kingdom, French client state, and Prussian province. His father was a master carpenter, and his childhood was spare (he later regretted the lack of Christmas presents), but relatively comfortable (Rush, 1929). According to a biographer, one fond memory that he would later recount was the receipt of an ABC book with a rooster and eggs on the cover containing the words "early the rooster crows and early starts to learn" (Rush, 1929). Whether this experience may have influenced his later work is unknown but intriguing to speculate! At age 16, he followed his older brother to medical school at The University of Göttingen, then part of the Kingdom of Hanover. Following Napoleon's abdication in 1814, Hanover was ruled in "personal union" by the British Kings George III and later George the IV. This practice ended, however, when Queen Victoria ascended the throne as Hanoverian law prevented a female from becoming monarch while a male-line successor lived.

In Göttingen, Berthold received his medical degree and spent the first years of his postgraduate training visiting with the outstanding medical and natural scientific men of his era in other German cities and in Paris. He briefly practiced medicine but apparently possessed a restless mind that brought him back to science, and eventually he became a professor and the director of the zoological division of the museum at Göttingen (Loriaux, 2016). Although he is most famous, at least in endocrinological circles, for his testicular transplantation studies, he also published on a wide variety of other topics including myopia (of which he suffered), hair formation, the structure of the head bones in gnawing animals, the actions of mercury on the salivary glands, and the anatomy of the thyroid gland of the parrot; he also published a paper with Robert Bunsen (inventor of the eponymous laboratory tool) describing the use of hydrated iron oxides for the treatment of arsenic poisoning. Berthold also mentored, among others, Carl Bergmann who studied body heat regulation and would go on to coin the terms “poikilotherm” and “homeotherm” (Loriaux, 2016; Medvei, 2012).

But most importantly for the history of behavioral neuroendocrinology, Professor Arnold Adolph Berthold demonstrated experimentally that a then unknown secretory product of the testes was required for the development of a cockerel into a rooster, both morphologically and behaviorally. In sharp contrast to hens or chicks, roosters often behave aggressively, are physically larger than hens, and have characteristic plumage; roosters also direct sexual behavior towards hens and crow. Capons, male chicks that have been castrated early in life, do not exhibit these rooster-typical behaviors or morphological characteristics. The behavioral and physical differences, among roosters, hens, capons, and immature chickens were likely familiar to Berthold (Berthold, 1849) (Fig. 1.1).

Although the precise motivation for Berthold’s experiment is not known (i.e., it is not clear that he performed this experiment for the same reason that modern behavioral endocrinologists would have; see below), he employed an approach that would become central to the field of behavioral endocrinology: that is, removal and replacement of the source of a hormone comprised three groups. The first group was caponized (i.e., the testes were removed early in life) and as expected these birds acquired the morphological and behavioral characteristics of capons. The birds in the second group were also castrated, but Berthold reimplanted one testis from each bird back into its abdominal cavity (chicken testes are located in the abdomen) cutting all the vascular and neural connections. Birds in the third group were also castrated, but after the testes were removed, Berthold placed a single testis from each bird into other birds’ abdominal cavities. The birds in both groups in which a testis was reimplanted (either an autograft or allograft) developed normally as roosters. Critically, when the birds were dissected, Berthold discovered that the reimplanted testes had developed vascular connections to the viscera, had nearly doubled in size (an early example of compensatory hypertrophy), and contained mature motile sperm.

Based on these results, Berthold drew three major conclusions from this work. First, the testes could be successfully transplanted and reestablish a vascular supply. Second, the implanted testes could produce sperm, and if properly connected to sexual organs, Berthold argued that they could still reproduce. Third, that because vascular, but not neural connections, had been reestablished, that neural inputs were not required for the normal function of the testis. To account for these findings, Berthold proposed that a “secretory blood-borne product” of *the transplanted testes (productive Verhältniss der Hoden*) was responsible for the typical development of the birds in the second and third groups (Forbes, 1949).

As noted, Berthold’s experiment has been credited as the genesis of the field of endocrinology (and of behavioral neuroendocrinology). However, Berthold’s intriguing demonstration of nonneural control of behavior was apparently not embraced with any enthusiasm by his scientific contemporaries; we find no citations to his paper for nearly 60 years after its publication. In addition to his research activities, Berthold authored a well-known physiology textbook, *Lehrbuch der Physiologie des Menschen und der Thiere* (*Textbook on the Physiology of Humans* *and Animals*) (Berthold, 1849). His textbook makes it apparent that Berthold was a proponent of the pangenesis theory of inheritance. This theory, endorsed by many biologists prior to the discovery of how chromosomes and genes function, held that all body parts actively discharge bits and pieces of themselves into the blood system, where they are transported to the ovaries or testes and assembled into miniature offspring resembling the parents. Moreover, it was thought that resorption of sperm from the testes was necessary for maintaining the secondary sexual characteristics of males. Because of this theoretical stance, Berthold had two concepts at hand when evaluating the results of his testicular transplantation study: (1) various parts of the body release specific agents into the blood, and (2) these agents travel through the blood to specific target organs.

Although his work, in retrospect, served as the first study to use several modern behavioral endocrinology techniques, including extirpation and replacement and monitoring of both behavioral and anatomical endpoints, at the time, the understanding of the role of the gonads in sexual development and behavior was understood quite differently than in the modern conception. Unfortunately, there is no introduction to his study, which reads much like a slightly elongated abstract, and it took many years and a great deal of inference from Berthold's other published work, to determine the motivation for and underlying premise of the experiment (Forbes, 1949; Quiring, 1944).

The role of castration in the development of animals had been known since antiquity, but the mechanisms for the behavioral and morphological consequences were unknown. In the eighteenth century, however, John Hunter (1718–1783), a Scottish physician, surgeon, medical researcher, and physiologist had performed critical experiments that may have influenced Berthold. Although the results were never published (at least by Hunter), he had transplanted spurs (claws) from hens onto a cock's comb and reported that the comb grew to the larger size typical of males. Spurs transplanted into a hen did not lead to comb hypertrophy. Further, in a study rather entertainingly published in his book *The Natural History of Human Teeth* (he had also implanted a recently removed human tooth into a cock's comb, preserved samples of which are still housed at the Hunterian Museum in London) (Hunter, 1771), Hunter successfully transplanted a testicle into the abdomen of a hen. Hunter was more interested in what was called at the time the "vital principle" which he held to be responsible for the survival of the transplanted tissue than in any conception of an endocrine mode of action (Jørgensen, 1971). Nevertheless, these experiments which Berthold mentioned in 1849 suggest that he was interested, at least in part, in the physiological changes that would occur in the testicle itself.

That the testicular transplant work was not followed up either by Berthold himself (he died 12 years later in 1861) or the broader scientific community is perhaps a bit puzzling. One potential answer, however, is that Rudolph Wagner, an anatomist, and physiologist, who would head the medical faculty at Göttingen while Berthold was on the faculty there, did attempt to replicate the experiments and was unable to do so as many testicular transplants failed to engraft (Loriaux, 2016; Forbes, 1949; Benedum, 1999). These difficulties, moreover, were not unique to the avian model system as similar experimental failures were reported in both amphibians and mammals (Medvei, 2012). It is unknown though tempting to speculate that his department heads' inability to replicate his work made continuing this line untenable and perhaps even led Berthold himself, to discount the work. Given the broad range of topics he addressed, it is also possible that Berthold simply lost interest and moved on to another problem or perhaps his failing health in the early 1850s curtailed his research (Benedum, 1999). What is known, however, is that interest in Berthold's work was not revived until a half century later following Charles Edouard Brown-Sequard's ideas surrounding testicular rejuvenation. Scientific discovery always builds on the work of earlier thinkers. Berthold's ideas were neither completely original nor fully modern but instead serve as a critical early step to the modern conception of endocrine function.

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Frank Lillie

2

Jacob R. Bumgarner

Abstract

Frank Rattray Lillie was an embryologist and endocrinologist of the nineteenth and twentieth centuries. His meticulous experimentation and carefully constructed scientific ideologies led him to become one of the first scientists to identify the mechanisms of sexual differentiation during development. The research he conducted throughout his career at the University of Chicago and the Marine Biological Laboratory covered an array of topics and questions, leaving a memorable and impactful legacy of scientific contributions. Lillie's early career focused on marine embryology, where he provided extensive descriptions of the characteristics and mechanisms of embryonic development in numerous species. Most importantly, Lillie also was the first scientist to exhaustively characterize and provide mechanistic insight into bovine freemartinism. More than just a scientist, Lillie was also a successful leader, administrator, and educator. In his positions at the University of Chicago and the Marine Biological Laboratory, he advanced education and research initiatives in addition to promoting democratic scientific environments. His early contributions to the field of sexual differentiation and his development of sex hormone research initiatives permanently shaped the burgeoning field of neuroendocrinology.

Keywords

Frank Rattray Lillie · Lillie · Freemartin · Sexual differentiation · Sex hormones · Marine biological laboratory

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Childhood and Family History

Frank Rattray Lillie was born in Toronto, Ontario, on 27 June 1870, to mother Emily Ann Rattray and father George Waddell Lillie. From Lillie's own account, his mother was a stay-at-home mother who dedicated her time to her family, church, and friends. His father was an accountant and a pharmacist. Although Lillie's parents did not seem to express interest in academics or intellectual pursuits, there was a clear pedigree of academia, science, and theology in Lillie's family history (Willier, 1957).

Lillie's paternal grandfather, Adam Lillie, studied at the University of Glasgow, had a passion for Greek literature and at one point studied Sanskrit at the University of Toronto. Adam's main passion in life was theological research and Christian education under the Congregational church. Adam served as a missionary in Toronto and founded the "Congregational Academy" at the University of Toronto in 1840, where over the next 24 years, he and his tutor would teach 64 students. In honor of his contributions to the Congregational church, the University of Vermont granted him an honorary Doctor of Divinity in 1854. In 1864, the college of the Congregational Academy was moved to the McGill College; Adam Lillie remained principal of the college until his death in 1869 (Eddy, 1976).

Lillie's maternal grandfather, Thomas Rattray, was the son of the famous Scottish pastor and astronomer, Thomas Dick. Thomas Rattray would devote his life to theology, serving as a minister first in Massachusetts and later in Ontario. As with his uncle, Thomas Lillie also had an interest in the natural world and similarly practiced amateur astronomy (Willier, 1957).

In common with many other prominent scientists, Lillie was interested in the natural world from a young age. In a written account, Lillie described his interest in "object lessons" while attending the Provincial School of Education in Toronto as a child. In one account, he remembers being at the age of 10 and learning in a school lesson that water would expand upon freezing (Willier, 1957). Later, on a cold winter night, he would test this phenomenon by filling a bottle with water, corking it, and leaving it outside while he slept. Lillie woke up in the morning to find with delight that the expanded ice had caused the bottle to shatter, confirming the lesson he had been taught in school. This early example of empirical testing and observation would foreshadow the type of scientist that Lillie would eventually become.

Education and Family Life

Lillie's grandparents' influence over his life extended beyond the development of his interest the natural world and academics. This was clear as he began his undergraduate education at the University of Toronto in 1887. Because both of his grandfathers were devoted to ministry and theology, there was some expectation that Lillie would study theology. During his undergraduate studies, Lillie hoped to maintain a personal separation between his scientific and religious views. He recalls discussions with a close friend on the cognitive dissonance that the subject of evolution caused in relation to his religious views learned as a child. Indeed, early after graduation, Lillie would spend some time as a minister in a Presbyterian church. However, he would later abandon the ministry and religion, writing that "science won out" (Willier, 1957).

While at the University of Toronto, Lillie chose to pursue a degree in Natural Science. His early studies included chemistry, geology, and biology. During his senior year of undergraduate studies under the guidance of Professor Ramsay Wright and Dr. Archibald Macallum, Lillie's career-long interest in embryology would begin. The summer after graduating from the University of Toronto in 1891, Lillie moved to the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts, to study embryology with Charles Otis Whitman (Moors, 1948).

During his first year at the MBL, Lillie studied alongside several prominent scientists of the time. Under the guidance of Whitman, Lillie would earn his doctorate studying cell lineages and the fate of blastomeres in organ development in the mussel *Unio* (Moors, 1948). During his second year of doctoral studies, Whitman took a chair appointment at the newly founded University of Chicago. Lillie would follow Whitman and earn his doctoral degree in Zoology at the University of Chicago in 1894. In 1893, Lillie helped Whitman to develop the MBL's first embryology course. One year later, Whitman would become the director of the course. In 1895, Lillie married Frances Crane; together they would have six children and adopted an additional three children (Wellner, 2009). His wife's brother, Charles R. Crane, would eventually play a prominent role in the financial backing of the development and expansion of the MBL (Lillie, 1944).

A Distinguished Career

Lillie's academic and administrative career alone could warrant an entire chapter to describe. After his doctoral graduation in 1894, Lillie moved to serve as an instructor at the University of Michigan and then in 1899 briefly taught at Vassar College in New York. He returned as an assistant professor to the University of Chicago in 1900, was promoted to associate professor in 1902, and earned tenure in 1906. After Charles Whitman's death in 1910, Lillie would become the Chair of the Department of Zoology at the University of Chicago. He was later named the Andrew MacLeish distinguished Service Professor of Embryology in 1931. He then served as dean of the division of biological sciences from 1931 until his retirement in 1935.

In addition to his career at the University of Chicago, Lillie held a concurrent career at the MBL. He started as an assistant director of the MBL from 1900 to 1908. He was then promoted as the director in 1908, where he remained until 1926. He was the president of the corporation and board of trustees from 1925 to 1942. Following this, he served as *emeritus* president until his death in 1947. Lillie's contributions of the MBL led it to become a democratic and internationally renowned research institution that remains active to this day.

Moreover, from 1935 to 1939, Lillie was the president of the National Academy of Sciences. From 1935 to 1936, he was the chairman of the National Research Council. He was the president of the Oceanography Institute next to the MBL from 1930 to 1939 and served as the managing editor of the Biological Bulletin from 1902 to 1926. Finally, Lillie's contributions earned him honorary degrees from the University of Toronto, Harvard, Yale, and Johns Hopkins University (Willier, 1957). Lillie was clearly an opportune man capable of impressive leadership.

Research Overview

Lillie could be primarily described as an embryologist, as he focused most of his research on the intricacies of embryonic development. Yet much as his administrative career, his embryological research was not confined to a single context. During his tenure at the University of Chicago and the MBL, Lillie studied the development of several organisms. Throughout the 45+ years of his research career, Lillie's expertise as a scientist would impact numerous subdomains of embryology, including fertilization theory, embryonic spatial and cellular organization, and sexual differentiation. Much of his recognized research can be distilled into four main categories: marine embryology, chick development, freemartinism, and sexual differentiation.

Marine Embryology

Inspired by the work that he conducted as a graduate student in Whitman's lab, Lillie's early work focused on the embryonic development of the mussel *Unio*. In several works published between 1893 and 1909, Lillie detailed the development of *Unio* and other species. His work on *Unio* exhaustively described egg polarity, centromere organization, fertilization localization, chromosomal organization, cellular cleavage planes, and cell lineage and fate (Lillie, 1901).

During this early career stage, Lillie also described the development of other species, including *Chaetopterus pergamentaceus*, a segmented worm. In several papers, he describes that the polarization of the egg of this species is dependent on the "ground substance" or the cellular membrane structure of the egg (Lillie, 1909a, b). Another study of this species detailed the ability for varying potassium chloride concentrations to induce cellular differentiation and organ development even in the absence of fertilization (Lillie, 1902). With this paper, he began laying the framework for a theory that he would later develop on the nature of fertilization.

As with his other lines of research, Lillie's scientific creed led him to constantly develop new hypotheses and frameworks to explain embryonic development and fertilization. For example, he was able to determine that egg polarization, nuclear division, cellular cleavage and differentiation, and cellular cleavage are all independent processes, but that typical development is dependent on the correlative timing of these processes (Lillie, 1902). He presented a hypothesis that there was an adaptive function to the organization of embryonic cleavage. In this hypothesis he argued that different features of cleavage produced adaptive structures that were based on the future needs of larvae in their environments (Lillie, 1899).

Finally, one of Lillie's other notable contributions to the early field of embryology was his "Fertilizin Theory," which he formulated in a series of work from 1910 to 1921. In this publication series, Lillie characterized fertilization in numerous species, including the sea urchin *Arbacia*. His developed "Fertilizin Theory" related to his discovery of what he dubbed *fertilizin* and *anti-fertilizin*, the extracellular material that covered eggs and sperm, respectively (Lillie, 1913). This theory encompassed the species-specificity, sperm and egg linkage, and egg activation aspects of fertilization (Lillie, 1914).

The extensive publication record that Lillie produced in this field is a legacy that any scientist would be proud to have. Yet, his focus on marine embryology is only a piece of his entire publication legacy.

Chick Embryology and Sexual Differentiation

In addition to the marine embryological research that Lillie conducted mainly at the MBL, Lillie became interested in sexual differentiation. As a true testament to his logistical and scientific fortitude, the research he conducted on sexual differentiation at the University of Chicago would occur simultaneously to his marine research at the MBL.

Lillie's interest in the mechanisms of sexual differentiation began around the time when much of his work at the University of Chicago was focused on teaching and chick development. After starting his faculty position at the University of Chicago in 1900, Lillie taught courses on embryology for undergraduate, medical, and beginning graduate students. In these courses, he used chicks as a model system to describe development. He felt that studying a single organism's development in detail served as an ideal introduction to the field of embryology and that chicks were the ideal organism to achieve this goal (Wellner, 2009). As a result of his devoted time to the undergraduate courses, Lillie published his introductory textbook to embryology: *The Development of the Chick*, "meant for the use of beginners in embryology" (Lillie, 1908). Additional revisions of this textbook would follow in the decades after its original publication, and it would be widely used as one of the best resources on chick development (Watterson, 1979).

Lillie did not publish extensively on chick development, but his work on this topic furthered his understanding on the fine-tuned sensitivity of the development process. In his experiments, he observed that ablation or perturbation of certain embryonic structures would eliminate the presence of these structures in adulthood or even completely impair overall development (Lillie, 1903). He also described the importance of some embryonic organs for the development of others as a "correlative differentiation" process. It is possible that this understanding of the linear and irreversible aspects of embryonic development led to his early conceptualizations of sex development and sex differentiation. In his first publication on the topic of sexual differentiation, Lillie seemed to have been aware that sexual differentiation was tied to early development, writing that "sexual differentiation is a phenomenon of irritability or response to stimulus, which lasts throughout the life history of the growing organism" (Lillie, 1907). Lillie seemed determined to identify the cause of sexual differentiation.

Freemartinism

One of Lillie's most famous contributions to the emergent field of endocrinology may have happened because of familial and geographical serendipity. Lillie was one of the first scientists to characterize embryonic sexual differentiation. Lillie's family owned a purebred cattle farm in Wheeling, Illinois, and it was here that his fascination with freemartins would begin. This fascination was accelerated when in 1914, his farm manager sent him a pair of calf fetuses twins still encased in their membranes (Watterson, 1979).

Freemartins are female cattle that are born with a male twin. Although these female twins appear to be typical females externally (typical external genitalia and mammary gland development), they are almost always infertile. They often have gonads that more closely resemble testes than ovaries, and the internal genitalia tracts are typically altered. Prior to Lillie's research on the topic, it was understood that freemartins could only be born as twins to a male. Despite freemartins being well-known throughout history, the precise mechanisms responsible for producing this type of animal were unknown.

After receiving the first pair of twins, Lillie began an extensive characterization of freemartins, thanks to the proximity of a cattle slaughterhouse to the University of Chicago. Lillie was able to convince the foreman of this slaughterhouse to notify him when cow uteri were found containing twins. Then, thanks to his relationship with his family farm, Lillie was able to quickly collect these uteri and perform careful dissections. One of his students recounts seeing him "garbed immaculately in a white gown and wearing rubber gloves, examining and dissecting pregnant uteri containing young twins…" (Willier et al., 1948).

Over the next 2–3 years, Lillie's careful dissections and diligent observations would bear two seminal publications. First in 1916, he published "The Theory of the Free-Martin," in *Science* (Lillie, 1916). In the publication, he corrects the previous conception that freemartins were monozygotic male twins that failed to develop external genitalia. Instead, his observation of two corpora lutea indicated that the freemartins were in fact a dizygotic twin. He then used the expected sex ratio of the birthed twins to confirm the observation that the freemartin twins were in fact female. Lastly, he describes that the twins have connected arterial and venous vascular systems. From the observation that the females only become freemartins in the presence of a male twin, he determines that the effect of the male on the female was "unquestionably to be interpreted as a case of hormone action" (Lillie, 1916).

In 1917, Lillie published a follow-up definitive and exhaustive description of freemartin calves (Lillie, 1917). In this publication, he describes freemartins as a form of a natural experiment that allowed for greater insight into the problem of sex-differentiation and sex-determination. His results lead him to conclude that sexual differentiation in mammals is largely determined by humoral sex hormones present in the embryo. Moreover, he also characterizes the effects of the putative sex hormones on duct differentiation. In typical undifferentiated fetuses, there are two sets of reproductive tracts present: the Wolffian and Müllerian ducts. In females, the absence of fetal androgens causes the Wolffian ducts to regress, and the Müllerian ducts will develop into the fallopian tubes, the uterus, and the upper vagina. In males, the presence of circulating androgens leads the Müllerian ducts to regress and cause the Wolffian ducts to form the seminal vesicles and vas deferens.

Lillie concluded that the presence of the putative sex hormone (at the time, no sex hormones had been isolated) that was being secreted by the male twin was leading to atypical development and prevented regression of the Wolffian ducts in the females, leading to a dysfunctional reproductive system and ultimately freemartinism. Lillie observed that the freemartin phenotype was greater when earlier vascular connections were made between the fetuses and that male development was almost always typical (Lillie, 1917).

Lillie's careful and tireless descriptions of freemartins would permanently sway the field of embryology. From his studies, he was able confirm his belief that sexual differentiation occurred during early development. Moreover, his observations on freemartins hold steadfast even by today's scientific standards.

Brown Leghorn Sexual Differentiation

After his discoveries on freemartins, Lillie then moved to organize a research program that focused on the isolation of sex hormones to examine their roles in sexual differentiation (Watterson, 1979). Lillie's own contribution to this program focused on the role of female sex hormones and thyroxin in feather development in the Brown leghorn fowl species. In one publication with Mary Juhn in 1932, Lillie and Juhn described the role that injected estrogen had on female feather pattern development and plumage (Lillie & Juhn, 1932). In this same publication, the role of thyroxin on male plumage was also extensively detailed. Lillie's contributions to the field of endocrinology and sexual differentiation would continue until his retirement.

Involvement in the Eugenic Society

As an unfortunate mark on Lillie's history, it is apparent that he subscribed to eugenic ideologies that were popular at the time. He held membership in the Chicago Eugenics Education Society, was a committee member of the Second International Eugenics Congress, and was on the advisory council of the Eugenics Committee of the United States (Wellner, 2009). According to Wellner (Wellner, 2009), "In the early 1920s Lillie envisioned an Institute of Genetic Biology that would gather data to examine population problems, public health, and social control, but this never came to fruition."

In contrast, it is also reported that Lillie emphasized the recruitment of African American students to the Zoology program at the University of Chicago (Allen, 2008). This effort included the recruitment of Ernest Everett Just, a graduate student and eventual lifelong friend of Lillie; Just would become a well-renowned scientist in the fields of fertilization and development. Nonetheless, it is important to contextualize Lillie's life outside of his contributions to research and remember the historical foundations that modern science stands upon.

Conclusion

Frank Lillie was an esteemed and well-rounded scientist, publishing over 100 communications and research articles throughout the duration of his career. His scientific fortitude, meticulous observations, and natural curiosity helped him to develop numerous veritable theories and make many monumental discoveries, many of which remain credible today. In particular, his contributions to the understanding of freemartins are discussed in undergraduate and graduate courses today (Nelson & Kriegsfeld, 2022). Lillie's view of the environment as a natural source of experimentation will always resonate with future scientists who look to find answers hidden in plain sight.

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Calvin Perry Stone

3

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Abstract

Calvin Perry Stone (1892–1954) was an American psychologist who is most recognized for his work in comparative and experimental psychology, though his research focused primarily on the nervous system and behavior. He is widely recognized for his contributions to our understanding of sexual behaviors in males and the physiological mechanisms that regulate this behavior. His studies using castration and ablations made it abundantly clear that hormonal influences, particular circulatory factors originating in the testes, were of importance to the expression of male sexual behaviors.

Keywords

Castration · Male sexual behavior · Testes

Calvin Alvin Stone was a pioneer in the physiology of reproductive behaviors. Born February 28, 1892, on a farm outside of Portland, Indiana, Stone was the youngest son and seventh of eight children born to Ezekial and Emily Brinkerhoff Stone. His paternal family, the Stones, were North Carolinians of English descent who moved to Indiana by way of Ohio. The Brinkerhoffs, of Dutch descent, settled in New York before gradually moving west, through Pennsylvania and Ohio, reaching Indiana in the late nineteenth century (Pickren, 2006).

By all accounts, Stone grew up in a caring and nurturing environment alongside his mother, sisters, and brothers. His mother played a primary and formative role in

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