Robert W. Goy

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Abstract

Phoenix, Goy, Gerall, and Young's 1959 publication radically changed the field of hormones and behavior which focused on investigating short-term hormonal activation of sexual behavior. The paper's demonstration that fetal testosterone exposure produced long-term behavioral change led to the Organizational Hypothesis that exposure to androgens during pregnancy permanently altered adult behavior. Robert W. Goy, who came to the WC Young lab with a history of studying conditioning, seemed an unlikely contributor to this revolutionary hypothesis. After joining the Young lab, Goy quickly mastered hormonal research, becoming one of the founders of the Organizational Hypothesis. The hypothesis was controversial and Frank Beach, in particular, publicly argued that hormones did not permanently alter brain development. Goy defended organization, as evidenced in an extensive private correspondence with Beach. In 1976 Beach publicly conceded that the organizational hypothesis was correct. Young, Goy, and Phoenix moved from Kansas to the Oregon Regional Primate Research Center (ORPRC) to develop studies with nonhuman primates and to investigate the development of sex differences in social behavior. With Young's untimely death in 1966, Goy became the head of the ORPRC lab and director of the Division of Reproductive Physiology and Behavior. In 1971 he became director of the Wisconsin Regional Primate Research Center (WRPRC), where he continued developmental studies of monkeys. These studies demonstrated that administering androgens prenatally, depending on timing and dosage, could masculinize reproductive anatomy without also masculinizing behavior and vice versa. Goy was an important founder of behavioral neuroendocrinology and promotor of the role that hormones played in development.

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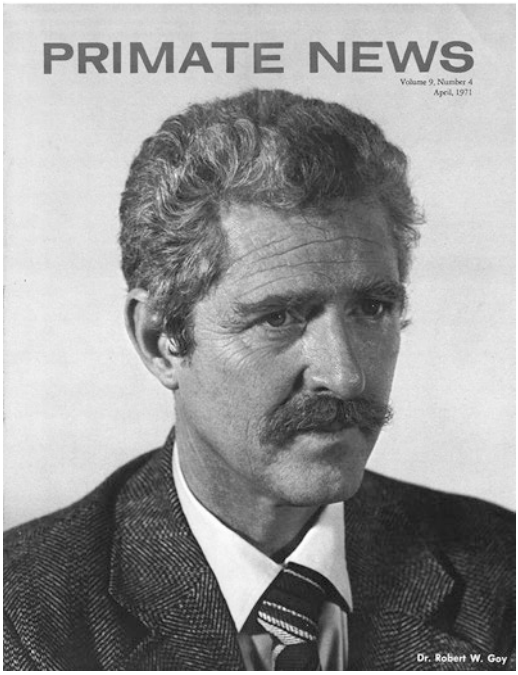

Robert W. Goy, Ph.D. in 1971 on the announcement of his leaving the Oregon Regional Primate Research Center to become the Director of the Wisconsin Regional Primate Research Center. (Photo credit: Oregon National Primate Research Center)

Most behavioral neuroendocrinologists know of Robert W. Goy (Bob) as one of four authors on the 1959 paper from W.C. Young's Kansas laboratory that permanently altered the study of what became behavioral neuroendocrinology (Phoenix et al., 1959). This single study argued that hormones not only had short-term effects that activated behavior but were also involved in organizing the development of the substrate of behavior biasing the individual's development and adult behavior. This completely new type of hormonal action, organizational, significantly expanded the endpoints and manner that hormones were investigated and how they might affect behavior. After this study hormones and behavior went from a discipline that

investigated how steroids activated behavior, primarily reproductive behavior, to one in which activational effects of hormones worked in concert with organizational effects of hormones in affecting a wide range of behavior. This view was not initially accepted by some investigators, but Goy was a powerful champion of the organizational hypothesis, helping it to become an essential principle of behavioral neuroendocrinology.

Goy's Early Career

Surprisingly, it was almost accidental that Goy joined the W.C. Young lab and became an author on the 1959 paper. Some historical background illustrates the serendipity in Goy's research career.

Born in Detroit, Michigan on 25 January 1924, Goy's father was a dentist and his mother a homemaker. Little record is available about Goy's childhood and early experience. In 1948 Goy received a BA in psychology from the Michigan State College of Agriculture and Applied Science (later to become Michigan State University) with a senior thesis entitled *"Learning of a Differential Response as a Function of Stimulus-response Asynchronism (!),"* which reflected his interest in behaviorism and its dominant influence on psychology. After graduation Goy left Michigan and pursued graduate study in psychology in the laboratory of Howard F. Hunt at Chicago University, receiving his PhD in 1953. Goy's dissertation, entitled *The effect of electro-convulsive shock on a conditioned emotional response: the relationship between amount of attenuation and strength of the conditioned emotional response* reflected the primary focus of Hunt's laboratory on conditioning (Hunt et al., 1953). While the dissertation was never published, it clearly reflected Goy's interest in conditioning, as well as the interaction between conditioning and physiological events. This was Goy's introduction to what later would become behavioral neuroscience, and it is a short distance from behavioral neuroscience to behavioral neuroendocrinology. None of these terms were in vogue at that time and there is no evidence that Goy was aware of what soon became hormones and behavior.

After receiving his PhD in 1953, Goy, along with his wife Barbara, moved to Hot Springs, Arkansas, to start postdoctoral work in the laboratory of Keller and Marian Breland, two behaviorists who had studied with B.F. Skinner and are credited with creating the first commercial application of behaviorism (Breland & Breland, 1951). They set out to revolutionize animal training, which they did using operant techniques to train animals to perform tasks not native to the animals, such as a guitar-playing duck, a baseball-playing chicken, and many others. Each activity had an operant box where the animal would perform the task each time a cue was given. Initially, the Brelands developed these show boxes for the Larro-feed division of General Mills, and the boxes were placed in feed stores and used in television commercials. Some boxes were designed to take coins and were placed in penny arcades and fair exhibits where a coin dropped into the apparatus became the cue to perform whatever the animal had been trained to do. They created Animal Behavior

Enterprise (ABE) and left Minnesota and moved to Arkansas. Although they published some research, *The Misbehavior of Organisms* (Breland & Breland, 1961), being one that introduced the concept of instinctual drift, which argued that over time animals' behavior would drift towards instinctual behavior to the detriment of conditioned behavior. This contradicted behaviorist dogma, which argued that animals build behavior solely by responding to reinforcement contingencies, whereas the Brelands showed that the same contingencies produced different behavioral responses depending upon the species studied. Goy had an enduring interest in behaviorism, as was common in psychology of the 1950s, and it seems likely that it was the Breland's focus on behaviorism and the availability of a position that attracted Goy to Arkansas. There is no evidence that Goy knew anything about the W.C. Young Lab about 450 miles North in Lawrence, Kansas, or anything about hormones and behavior.

Elliot Valenstein, a graduate student in W.C. Young's laboratory, was, like Goy, a Michigan native, who graduated from the University of Michigan. While Goy was in Chicago, Valenstein's wife, Theresa, met Goy and his wife at a meeting, and she reported to Elliot that she had met a very nice couple in Chicago (Baum et al., 1999). Some months later Valenstein and his wife were driving from Lawrence, Kansas, to a scientific meeting in Galveston, Texas. As described by Valenstein (Baum et al., 1999), their route took them through Hot Springs, Arkansas, which they remembered was where the Goys lived. They called the Goys and were invited to visit them. They were surprised when they arrived at the Goy's house that it appeared that most of the Goy's possessions were on the porch and that Bob and Barbara were preparing to leave (Baum et al., 1999). Goy could not tolerate doing commercial animal training for the Brelands instead of research. Even though the operant conditioning was automated, the ABE was so successful that little or no time was left for research. Typical of Goy when he was fed up with some activity, he would make a snap decision, even if it meant an uncertain future. Thus, the Goys were leaving Hot Springs and heading to Chicago to seek Hunt's help in finding a position. According to Valenstein in meeting with the Goys in Hot Springs, he wondered out loud whether Young would hire Bob. A few weeks after moving to Chicago, Goy asked Valenstein whether Young would hire him. It turned out that Young, who was in an anatomy department but studied behavior, had been thinking of adding another psychologist in a postdoctoral position (Baum et al., 1999). Thus, Goy joined the lab in 1954, followed soon by Charles H Phoenix in 1954 and Arnold A. Gerall in 1956.

Goy entered the Young lab supported as a Public Health Service Research Fellow of the National Institute of Mental Health. His entry must have been daunting; Goy at that time had never published a scientific paper and had no experience with hormones, behavior, or anatomy, which was a problem for a position in a department of anatomy. The field Goy was entering was then dominated by Frank A. Beach and especially by W.C. Young. In the 1930s Young and collaborators had shown that the estrous behavior of female guinea pigs varied with the state of her ovaries. Steroid assays were not to come about until 1967; thus, the anatomy of the ovary, which indicated follicular development, ovulation, and corpus luteum formation served as

a proxy for the underlying hormonal changes. Young's lab in the mid-1930s developed the first hormonal replacement therapy for ovariectomized guinea pigs (Dempsey et al., 1936) demonstrating that the female had to be exposed to at least 24 h of exogenous estradiol followed by a single injection of progesterone which activated the female's expression of lordosis indicating her sexual receptivity. This hormonal regimen has been found effective in multiple rodent species, but does not work in many nonrodent mammals, such as nonhuman primates and humans.

Goy was a quick study and rapidly integrated himself into the behavioral work as well as learning gross anatomy so that he could teach in the department. By 1957 Goy published his first paper and published five papers in total that year on a range of topics. Appropriately, Goy's first publication was as a co-author with Valenstein entitled *"Further studies of the organization and display of sexual behavior in male guinea pigs"* (Valenstein & Goy, 1957). The use of "organization" in this article might be seen as foreshadowing what was to come, but "organization" was not used in a manner having anything to do with hormones and simply meant how a behavior was put together, whether that organization resulted from experiential and/or physiological factors. This paper, published in 1957, was submitted for publication in October of 1955, a year after Goy arrived in the Young lab illustrating how rapidly Goy developed research. In the case of this article, he may have been invited to work on a topic already developed by Valenstein as part of his ongoing dissertation.

Goy's publications reflected an eclectic range of research interests ranging from the length of gestation (Goy, Hoar, & Young, 1957) in guinea pigs to the role of soma in sexual behavior (Goy & Young, 1957). Soma, a term that has fallen out of favor, refers to what we would now call the body but was used in more limited fashion in the Young lab becoming a synonym for neural systems. Goy's initial first-authored paper, with Young, "Somatic basis of sexual behavior patterns in guinea pigs: Factors involved in the determination of the character of the soma in the female," addressed what was meant by 'soma' and what factors might be considered relevant to understanding the role that soma played in behavioral effects of hormones. The paper starts with the following:

> … once the threshold necessary for hormonal stimulation has been reached, the character of sexual behavior displayed in response to that stimulation is determined by the nature of the soma or substrate on which the hormones act rather than by qualitative or quantitative variations in endogenous hormones. (Goy & Young, 1957, p.144)

This focus on the nature of the underlying substrate that is responsive to hormone action was only a hypothesis at this point and presented a relatively radical departure from the stimulus-response explanations used by behaviorists. Little was actually known at this time about the nature of soma and the central problem facing Young's lab was how to identify factors that determine soma and elucidate how hormones contributed to the nature of soma. This focus, however, asserted that there was a physical substrate underlying behavior and that substrate was likely neural.

Key evidence suggesting the consistent nature of the substrate comes from studies in the Young lab of two inbred strains of guinea pig. Strains 2 and 13 were the

last remaining strains from Sewell Wright's original inbreeding study (Wright, 1923). Goy and Valenstein led studies of these strains assessing their sensitivity to steroids for activating male and female sexual behavior (Goy & Young, 1956; Goy & Jakway, 1959; Valenstein et al., 1955). These studies showed strain differences in male and female sexual behavior and that these differences had high heritability, supporting the notion that the substrate underlying sexual behavior differed consistently between the strains. This provided the basis for identifying hormonal factors that could permanently modify the soma.

Phoenix, Goy, Gerall, and Young, 1959 and Beyond

At some point during the period from 1952 to 1958, Young focused his work on three things he wanted to accomplish in the coming years. Young had experienced a bout of cancer that was in remission, but according to Gerall (Gerall, personal communication, 2004), Young was convinced that the cancer would reoccur, which it did in 1965 (Goy, 1967). Young felt his time was severely limited (Wallen, 2004) and thus Young created the three goals. The first was to complete the third edition of *Sex and Internal Secretions*, which was the "bible" of hormones and behavior and which Young had taken over from Edgar Allen (Allen, 1932). Progress on the new edition was slow, but Young did complete it in 1961 (Young, 1961a). The second goal was to publish 100 research papers, which Young did. Third was to complete a study that would have a significant impact on the field of hormones and behavior. Bringing together a number of threads from previous studies, Young proposed investigating whether exposing genetic females to androgens prenatally would alter their behavioral development. It is not clear whether Young proposed that the prenatal effects of exposure to androgens would be permanent, but it likely was his hypothesis that the effects of prenatal androgens would differ from adult activational effects which are transitory. Young was aware of Vera Danchakoff's work in the middle 30s in which she injected testosterone directly into fetal guinea pigs and investigated their adult sexual behavior (Dantchakoff, 1938a, b). She reported that the injected guinea pigs showed genital masculinization as well as behavioral masculinization. Unfortunately, there was no control group and Danchakoff was apparently unaware that female guinea pigs show significant mounting behavior, which is increased by injections of androgens. Danchakoff's work foreshadowed the organizational hypothesis but was poorly controlled leading to little adoption of her views on hormones and development. Young, on the other hand, interpreted Danchakoff's work as demonstrating the possibility that prenatal androgens could permanently alter the development of the nervous system. This seemed to be an issue worth pursuing that might have a substantial impact on the field.

Exactly how the study was developed and how it was decided who would work on it is unclear. Gerall reports (Gerall, personal communication, 2004) that the investigators working on the project worked relatively independently; there were no lab meetings to develop the project or to discuss how the data would be analyzed. Even the final write up was done relatively independently with pages passed around

but reflecting essentially independent work. When the study produced evidence that suggested that prenatal exposure to androgens resulted in permanent behavioral masculinization of genetic females, there was disagreement about how to interpret this. One faction argued that the nervous system had been permanently modified, while the other faction argued that this was not the case and that androgens simply modified function and not anatomy. Young, in particular, argued that as an anatomist that there was no anatomical evidence to support the argument that prenatal androgens masculinized the nervous system as they did genitalia. This issue was unresolved when the paper was submitted to Endocrinology for publication. The legacy of not resolving this issue resulted in one of the striking aspects of the 1959 "organization" paper (Phoenix et al., 1959) in that it has two ending paragraphs that disagree with each other. The first, written by Goy (Gerall, personal communication, 2004) is as follows:

> The nature of the modifications produced by prenatally administered testosterone propionate on the tissues mediating mating behavior and on the genital tract is challenging. Embryologists interested in the latter have looked for a structural retardation of the Mullerian duct derivatives culminating in their absence, except perhaps for vestigial structures found in any normal male. Neurologists or psychologists interested in the effects of the androgen on neural tissues would hardly think of alterations so drastic. Instead, a more subtle change reflected in function rather than in visible structure would be presumed (Phoenix et al., 1959, Page 381)

Goy argued that the influence of prenatal androgen is on function instead of physical structure. In other words, androgen-influenced structural modification of the central or peripheral nervous system was rejected. Young proposed using the phrase "tissues mediating mating behavior" never letting the reader know what comprised those tissues. The penultimate sentence rules out that neural tissues are under discussion.

Gerall (personal communication, 2004) contributed the last paragraph which stated:

> Involved in this suggestion is the view that behavior may be treated as a dependent variable and therefore that we may speak of shaping the behavior by hormone administration just as the psychologist speaks of shaping behavior by manipulating the external environment. An assumption seldom made explicit is that modification of behavior follows an alteration in the structure or function of the neural correlates of the behavior. We are assuming that testosterone or some metabolite acts on those central nervous tissues in which patterns of sexual behavior are organized. We are not prepared to suggest whether the site of action is general or localized. (Phoenix et al., 1959, Page 381)

This paragraph leaves little doubt as to that the "tissues mediating mating behavior" are neural tissues. Young expressed little concern about the contrast between the two views arguing that history would decide which was correct (Gerall, personal communication, 2004). It is ironic that Goy championed the functional argument over the anatomical argument as he became known for his view that prenatal androgens modified the nervous system, having abandoned the functional argument by 1964 when Young et al. (1964) published "Hormones and Sexual Behavior" in *Science*. In

this article the authors argued that prenatal hormones modified the substrate that hormones acted on (soma) to activate sexual behavior. Soma was presumed to be neural tissue. Aside from Phoenix et al. (1959), the notion of altering function without altering neural anatomy was not argued by the Young lab. In addition to supporting the idea that hormones could alter neural anatomy, Young et al. (1964) argued for the more radical notion that these findings, obtained from nonhuman mammals, applied to humans as well, an idea that remains controversial to the present but identifies a primary driving force of Young's research program.

After the publication of the 1959 paper, Goy followed up with a study that expanded our understanding of the parameters of organizational effects of androgens. The primary concern, which would be addressed several times in Goy's career, was the timing of androgen exposure on masculinization and defeminization. Goy, Bridson, and Young et al. (1964) administered testosterone propionate (TP) starting at gestation day (GD) 15, 20, 25, 30, 35, 40, or 50 of the 70 day guinea pig pregnancy. TP was administered in different amounts and for different durations, from 15 to 30 days. Since TP was injected daily (5 mg/day for days 1–6 and 1 mg/day for the rest of the treatment), total androgen exposure varied between groups, varying from 40 mg to 75 mg. Androgen-exposed females and control males and females were gonadectomized as adults and tested for lordosis response to a sequential estradiol (E_2) and progesterone (P) regimen that activates female sexual receptivity in untreated females. It was apparent from the findings that one of the most critical variables affecting masculinization and defeminization of genetic females was the timing of the treatment. One hundred percent of females exposed to 15 days of TP treatment, starting on GD15, but only 44% of females whose TP treatment started on GD 30 became sexually receptive after the sequential E_2 and P treatment (e.g., the GD30 females had become defeminized). Duration of treatment (which also affected total TP exposure) also had an effect in that extending the duration of treatment to from 15 to 25 days resulted in 88% of the females started on GD15 becoming sexually receptive as adults, but only 8% of the females whose 25 day treatment started on GD 30 became sexually receptive. This was an important finding as it not only provided a replication of the 1959 paper's findings but also suggested that the developing nervous system had very specific periods of sensitivity to prenatal androgen (Young et al., 1964).

Monkey Studies and the Move to the Oregon Regional Primate Research Center

Soon after publication of the 1959 paper, the Young group in Kansas, now missing Valenstein and Gerall, who had both followed their independent lines of research, thought it important to investigate organization in a non-rodent species and settled on studies of rhesus monkeys. At the time there was no national primate research center program, so the group took advantage of other facilities to start monkey research. Phoenix moved to Cincinnati, OH where the Christ Hospital Laboratory had a small monkey colony that could be used to create timed pregnancies that they

thought would allow accurate timing of testosterone administration to the pregnant females (Baum et al., 1999). Phoenix was attempting to do something that had not been previously done and where there was little background information. His goal in Cincinnati was to create monkey pseudohermaphrodites by administering prenatal testosterone as had been done in the guinea pig.

Goy went to Madison, WI, and the laboratory of Harry Harlow who headed the Primate Lab of the Department of Psychology of the University of Wisconsin-Madison to learn how to observe juvenile behavior in monkeys. Leonard Rosenblum, a postdoctoral fellow in Harlow's lab, had collected the first data showing that juvenile males, long before puberty engaged in quite different behavior than did juvenile females, particularly, play and mounting behavior. Goy was to learn how to observe juvenile behavior to be used in evaluating Phoenix's pseudohermaphrodites to see if the females' juvenile behavior had been masculinized by prenatal TP. From a theoretical standpoint, this was a very important investigation as the juvenile behaviors that showed sex differences occurred during a time when the monkey's gonads are quiescent. Thus, these sex differences were not in hormonally activated behavior. If the females prenatally exposed to androgens showed a masculine pattern of juvenile behavior, then it would be irrefutable evidence that the difference in the treated females' behavior was not the effect of hormonal activation but reflected that the function of the nervous system had likely been modified by prenatal androgen exposure. Once modified hormones were not necessary for exhibiting behavior. If such effects were seen, then it could be interpreted as supporting Goys' original interpretation of the 1959 study but would integrate function with the actions of prenatal hormones.

The plan was to transport the treated pregnant females created by Phoenix by van from Cincinnati to Madison and place them under the care of Goy. The young were born in Madison and Goy observed and recorded their behavior in what became a long-term systematic study of their behavior (Baum et al., 1999).

This was a very risky project as little was known about monkey social behavior. In addition, steroid assays had not yet been invented so timing pregnancies had to be done using a calendar method that started counting with the onset of menstruation. It wasn't discovered until after the advent of steroid assays that the relationship between menstrual onset and ovulation was highly variable across females, but at the time there was no alternative. Phoenix was successful in creating the first pseudohermaphrodite monkeys in Cincinnati. The first images of these masculinized females and evidence that the juvenile behavior of pseudohermaphrodite females was masculinized appeared in Young et al. (1964). The process of creating these monkeys had been difficult, but it had been successful.

Fortunately for the Young lab the US government created a national primate center program to greatly increase laboratory primate research. In 1962 the Oregon Regional Primate Research Center (ORPRC) opened and recruited Young to create and direct a Division of Reproductive Physiology and Behavior. Young accepted and moved to Oregon in 1963. Part of the agreement with Young was positions for Goy and Phoenix who were also hired as Associate Professors. ORPRC became the only primate center with a division focusing on hormones and behavior and was the

only place in the world where the effects of prenatal androgen exposure on sexually differentiated behavior was being studied in both guinea pigs and rhesus monkeys.

The Young lab continued work in both guinea pigs and rhesus monkeys. As the only place where studies in both species were possible the lab recruited a number of graduate students and post docs. Several of the postdocs were Frank Beach PhD's (Lynwood Clemens, Norman Adler, Gray Eaton) reflecting the close association of the Beach and Young labs.

As Young had predicted his cancer did return leading to his death in April 1966, less than 3 years after he moved to Oregon. On Young's death, Goy became the director of the Division of Reproductive Physiology and Behavior and the principal investigator on the NIMH grant that funded the laboratory's work.

The Organizational Hypothesis and the Ramstergig

Publication of the Organizational Hypothesis in Phoenix et al. (1959) did not immediately have a noticeable influence on the field. During the first decade (1959–1969) after publication, the paper was cited approximately 50 times (Wallen, 2009). This likely reflects that until the publication of the hypothesis no laboratories were working on permanent effects of hormones on sex-specific behavior. Anatomical effects of prenatal steroids had been actively pursued by Alfred Jost (Jost, 1953) and Dorothy Price (Price et al., 1967), but behavior was not an endpoint in their studies. As the idea that hormones could permanently alter neural anatomy and function permeated the field of hormones and behavior, the impact of the 1959 paper increased dramatically. The field went from one that studied factors that affected hormonal activation of hormone-sensitive behavior to one that focused on two different but related processes, activation, and organization of behavior. This firmly established behavior as an important window into neural function.

Not everyone accepted the validity of the organizational hypothesis. Frank Beach argued strongly that steroid hormones during pregnancy or early development did not organize behavior. His objection to the organizational hypothesis culminated in the publication of a paper entitled "Hormonal factors controlling the differentiation, development, and display of copulatory behavior in the ramstergig and related species" (Beach, 1971), which was shockingly critical of the hypothesis. Interestingly, the only member of the Young laboratory who was criticized by name, was Gerall, which Gerall noted (Gerall personal communication, 2004). This may have reflected that Beach was concerned about the possible negative response the Young lab (now the Goy lab) might have. By the time the ramstergig paper was published Gerall had left the Young lab and started a faculty position in Tulane and thus his response to Beach's paper was of less concern than the rest of the Young Lab, Goy in particular. Beach and Goy extensively corresponded and Beach's concern about Goy's reaction is apparent in an undated letter to Goy that begins with "I send you the enclosed manuscript with some trepidation." The manuscript was a not-yet-published version of the Ramstergig paper that Beach was sharing with Goy (personal communication, Beach-Goy correspondence). The rest of the letter continues to elaborate on

Beach's trepidation, saying, for example, "What I hope does not need saying is that I have always held Bill Young in very high esteem and as a close personal friend." Later Beach writes "I sincerely hope that what I here intend to be a totally impersonal, objective and scientific critique will not be interpreted by you as a devaluation of your research or a personal assault." Beach was clearly aware that he might be stepping over a line with Goy, his good friend. The extent to which he had stepped out was apparent in a letter dated June 22, 1970, from Goy to Beach in which Goy, in his somewhat opaque style, described his reaction to the Ramstergig paper as follows (Beach-Goy correspondence): "The ramstergig was delightful, clarifying, and in some parts, hilarious. I especially liked the Sperry-type explanation for organization." [Beach had presented images of an organized and disorganized brain, that were actually of a frog tectum like those studied by Sperry.] Goy continued: "I have to admit that I dismissed some parts (with pique) as too banal, exaggerated, and misrepresentative, but then why shouldn't I? Keep up the good work. Charles and I hope next year to do a devastating rebuttal." Was Goy offended and if so, how much? I suspect Goy's graduate students would recognize his construction of very positive comments intertwined with negative comments leaving one to guess the depth and direction of Goy's true feelings. Personally, it took me several years in Goy's lab to realize that "I wouldn't do it that way" strictly meant "don't do it!" On 25 June 1970, Beach replied to Goy's letter with "I am …pleased to learn that you find you can at least tolerate the Ramstergig paper. I would have been greatly surprised if you failed to react quite negatively to some of the sections but am glad that this wasn't your overall response."

The Ramstergig paper again appears later in the Goy correspondence, brought up by Beach. Three years later, on 17 October 1973, Beach sent a mimeographed letter entitled "Verbatim Quotation" to both Goy and Phoenix. Whether it was sent to anyone else is not known. The letter had a quotation from 1948 and asked recipients to identify who made the statement, which addressed what type of actions hormones during "embryonic differentiation" exerted and contrasted activation effects on pre-existing "arcs," presumably neural, or as "… organizers inducing certain connections amongst special nervous centers." It appeared that Beach's intent was to show that the issues raised in Phoenix et al. (1959) moving the field to consider hormones as organizers or directors of development had already been raised in 1948. Goy and Phoenix both recognized that the quote was from work by Martins and Valle (1948) in a paper on micturition patterns in the dog, a behavior that ultimately convinced Beach that the hormonal organization concept was real. On 25 October 1973, Goy wrote Beach a defensive letter where he identified the source of the quotation and delineated all of the places, he had presented Martins and Valles findings and considerations, ending the letter with "I agree with your implied opinion that these workers should not endure further neglect by the scientific community, but they really haven't done much since then have they?" Interestingly, Martins and Valle (1948) paper published 11 years before the 1959 paper was not cited in Phoenix, Goy, Gerall, and Young (1959).

Beach replied on 5 November 1973 with "Whoa! Down boy, Down! I was just having fun when I sent out this quote from M&V but I can see from replies I received

from you and Charlie that I touched a nerve. … Guess my Ramstergig paper must have left a scar." Beach went on to describe his work on dog urination posture which is sexually dimorphic with females squatting and males lifting a leg allowing them to urinate to the side. Beach was finding that urination posture was affected by hormones during pregnancy, but did not require any activation by hormones, testosterone in particular. Beach added "To some extent it resembles your own evidence concerning sex differences in play in the pseudohermaphroditic female" (monkey). "The effects of early treatment are there, Brother, without any necessity for concurrent stimulation by exogenous hormones. Who was the idiot who claimed that all that prenatal treatment does is to change thresholds to concurrent hormonal stimulation???" In this letter Beach capitulates to the new paradigm that Goy has been championing since Young et al. (1964) that hormones do not simply have activational effects but also organizational effects that direct development. Goy's response 10 days later, while defensive is also typical Goy as after one reads his statement one is not completely certain of his argument. Goy writes "I have no scars from the Ramstergig paper, which I thought did a much-needed job of exorcising. While it did not put the devil in hell with as much artistry as Boccaccio, it at least removed God from the Heavens. I really thought you were worried about where the quotation came from…" Goy proceeds with a long description of all the cases where hormones have organizational, but not activational effects, including cases of dimorphic characteristics, such a canine size, where hormones appear to have no effects on the difference between males and females. Goy ends the letter with "… Please don't ever stop sending your little epistles, whether in anger or despair, or both."

Phoenix's response to Beach's query gives some idea of why Beach took the approach with the mystery quotation. Phoenix wrote to Beach that the Martins and Valle had not gone unnoticed "… nor did the following statement by an eminent scientist published 4 years later (1952): 'It is conceivable that prenatally secreted gonadal hormones might act as 'organizers', influencing the laying down of nervous connections which later are involved in the mediation of sexual behavior,' Beach (1952) Page 214. The author rejected the possibility." The 1952 paper was one of several points where Beach had data consistent with the organizational hypothesis but rejected that explanation. Instead, Beach saw the data as reflecting the effect of prenatal hormones masculinizing female genital anatomy, but not the neural structures underlying masculine sexual behavior (Baum 1990). Beach's dog urination studies led him to the realization, as he confessed to Goy (above), that the dog and monkey studies showed behavioral masculinization without the need of hormonal activation and were compatible with the organizational hypothesis. One can only imagine how challenging it must have been for Beach to realize that the construct that radically changed the field of hormones and behavior was once within his grasp, but he had rejected it.

Many date the resolution of the debate about the organizational hypothesis to 1976 at the Eastern Conference on Reproductive Behavior (ECRB) meeting in Saratoga Springs, New York. Goy and Beach agreed to participate in a roundtable on sexual differentiation where many anticipated verbal fireworks when each would

argue the position on organization for which they were known (Dewsbury, 2003). To the surprise of many, including myself, Beach announced that, primarily because of his dog work, he now agreed with Goy and Phoenix that hormones early in development organized neural structures (Dewsbury, 2003). The correspondence between Beach and Goy discussed previously suggests that Goy and Phoenix were not likely surprised by Beach's change of heart, though I never remember Goy ever suggesting it was a possibility that Beach would accept the organizational hypothesis.

After that meeting, the organizational hypothesis was widely accepted. Researchers clarified aspects of the hypothesis and sought organizational effects during other times than the fetal and perinatal period. The most promising time is pubertal organization when many species undergo substantial reorganization (Sisk & Zehr, 2005). These clarifications further defined the parameters of organization but didn't challenge the basic concept (Wallen, 2009). The field of hormones and behavior had been transformed from a field focused on hormonal switches that activated preexisting neural structures to one in which there were activational switches, but also hormonally directed permanent alterations to, and creation of, neural structures. Beyond championing the organization hypothesis, Goy had an impact on a variety of activities that influenced behavioral neuroendocrinology.

Director Wisconsin Regional Primate Research Center

In 1971 Goy was named Director of the Wisconsin Regional Primate Research Center (WRPRC), a position he held for 18 years. He moved his laboratory from Oregon to Wisconsin and succeeded Harry Harlow as director of the WRPRC. Goy brought the first behavioral neuroendocrine lab to the WRPRC. All was not smooth sailing though. In addition to being director of the WRPRC before Goy, Harlow was also director of the Primate Lab, which was part of the University of Wisconsin – Madison Psychology Department. Because Harlow was in charge of both facilities, it apparently was unclear what expenditures of the WRPRC, funded by an NIH base grant, were for WRPRC researchers and which served the Primate Lab researchers. NIH tasked Goy with clearly separating the two facilities (Goy, personal communication). This meant that services paid from, the WRPRC base grant, such as a nursery for infants, had to be put on a charge-back basis for Primate Lab researchers, leading to significant enmity between the Primate Center and the Primate Lab. The conflict between the Primate Center and the Primate Lab never really disappeared during Goy's 18 year tenure as director (Phoenix, 1999),

At Wisconsin, Goy initiated studies on how early experience affects the development of adult reproductive behavior in rhesus monkeys. He was the first to recognize that the standard laboratory rearing paradigm, invented at the University of Wisconsin by Harlow produced seemingly appropriate juvenile social behavior but deficient adult sexual behavior, particularly for males (Goy & Wallen, 1979). Goy developed a unique laboratory rearing environment using carefully selected 4–5 member groups of mothers and infants. The environment preserved important

aspects of the social environment a rhesus monkey would normally encounter in its natural habitat. With colleagues David Goldfoot and Kim Wallen, Goy demonstrated the important role that early experience plays in the expression of juvenile and adult sex differences in behavior. This research, in addition to continuing studies of the prenatal hormone role in behavioral development, advanced the notion that the prenatal hormonal environment produces behavioral predispositions which are then shaped and molded by early social context. In Goy's view, both biological and social influences were crucial to the development of masculine and feminine patterns of behavior.

Goy continued studies of monkey development and the role prenatal hormones had in the development of sex differences in behavior, advancing our understanding of the scope of organizational effects of hormones on behavioral development. What was met with skepticism in 1959 is now a central part of behavioral neuroendocrinology. Goy was present at the beginning. After serving 18 years as Director of the WRPRC, Goy retired in 1989 and died 14 January 1999, in Madison, Wisconsin.

Other Contributions to Behavioral Neuroendocrinology

Goy published over 110 refereed papers, each one making an important contribution to behavioral neuroendocrinology. He also was active in serving on NIMH study sections to assist in evaluating research, proposals I have selected some of his activities and several of his papers that were of particular importance to the field.

Editor of *Hormones and Behavior*

In 1969 Beach created the journal, *Hormones and Behavior*, edited by Beach, Richard Whalen, and Julian Davidson, members of Beach's lab (Wallen, 2020). *Hormones and Behavior* was the first journal dedicated to the emerging field of behavioral neuroendocrinology and developed into the primary outlet for behavioral neuroendocrinologists. From 1969 to 1986, the journal changed its structure, adding associate editors from outside of Beach's laboratory in 1973, the year that Goy was named an Associate Editor. In 1977 Goy became one of the Editors in Chief (EIC) along with Beach and Whalen. One characteristic that was constant until 1986 was that all EICs and associate ditors were men. Starting with Issue 3 of Volume 20, Beach became an emeritus editor and Goy and Whalen became co-EICs. With this issue four women were named associate editors signaling the start of a gender balance in the journal that continues today. Goy and Whalen remained as Co-EICs until 1997 when *Hormones and Behavior* became the official journal of the new Society for Behavioral Neuroendocrinology, a society that Goy had championed, and Michael Baum became the EIC (Wallen, 2020).

The Aromatization Hypothesis

In the penultimate sentence of the discussion in the 1959 paper, the authors raise the possibility that although they had demonstrated organization via prenatal testosterone exposure they presciently hedged their bets stating "We are assuming that testosterone or some metabolite acts on those central nervous tissues in which patterns of sexual behavior are organized" (Phoenix et al., 1959 page 381). Years later Reddy et al. (1974) demonstrated that fetal rat limbic and hypothalamic homogenates were capable of metabolizing testosterone into estrone through aromatization. Additionally, the level of aromatization was much higher in male than in female fetuses raising the possibility that testosterone's effects on sexual differentiation might be mediated by conversion to an estrogen (Reddy et al., 1974). McDonald et al. (1970) reported that treating castrated male rats with testosterone propionate (TP) reinstated sexual behavior, but treatment with 5α-dihydrotestosterone propionate (DHTP), a nonaromatizable androgenic metabolite of testosterone, did not reinstate male sexual behavior. This finding was later replicated by Whalen and Luttge (1971). These and other studies provided evidence that estrogenic metabolites, both during fetal development and in adulthood, were necessary for masculinization of behavior in rats, mice, and hamsters. The necessity of the aromatization of testosterone to an estrogen became known as the Aromatization Hypothesis and has been a central dogma of behavioral, neuroendocrinology since the late 1970s. Goy was interested in whether estrogenic metabolites of testosterone were necessary for reinstating male sexual behavior in guinea pigs as was the case in other rodents. With his graduate student, Pamela Alsum, they found that DHTP was as effective as was TP in reinstating male sexual behavior in castrated males. Furthermore, estradiol had no effect on reinstating masculine behavior (Alsum & Goy, 1974). At the same time as the guinea pig work was published so was a study by Phoenix (Phoenix, 1974) showing that long-term castrated male rhesus monkeys' sexual behavior was reinstated by DHTP or TP as was the case in guinea pigs. Additional evidence that aromatization of testosterone was not required was presented by Goy et al. (1988) who found that blocking aromatization of T by administering 1,4,6-androstatriene-3,17-dione (ATD), an aromatase inhibitor, concurrently with testosterone to castrated males did not prevent testosterone reinstating male sexual behavior. Further evidence that testosterone's effects on sexual behavior did not rely on aromatization was found in studies of prenatally androgenized females who had received either TP or DHTP during gestation. Goy along with his postdoc, Steven Pomerantz, and graduate students Marc Roy and Janice Thornton tested androgen-exposed females for evidence of behavioral masculinization and defeminization (Pomerantz et al., 1985; Thornton & Goy, 1986). Unlike all rodent species studied, primate females do not exhibit lordosis or have a behavior comparable to lordosis. Instead the primary female sexual behavior is sexual initiation or solicitation (Wallen, 1990). When genetic females were treated prenatally with either TP or DHTP, they displayed masculine sexual behavior as adults (Thornton et al., 2009). Strikingly when these females were treated as adults with estradiol and tested for sexual initiation and solicitation with adult males, both the TP- and DHTP-treated

females did not show solicitation and sexual initiation. Thus, unlike rodents where only aromatizable androgens would defeminize females, in monkeys either aromatizable or nonaromatizable androgens administered prenatally defeminized the female's behavior.

The Aromatization Hypothesis, while widely supported in short gestation (altricial) mammals, where much of sexual differentiation occurs neonatally, did not appear to apply to long gestation (precocial) mammals where sexual differentiation occurs primarily during gestation (Wallen & Baum, 2002). Of particular interest is that rhesus monkeys do not appear to rely on aromatization for either masculinization or defeminization of behavior. This makes it likely that estrogenic metabolites are not necessary for masculinization and possibly defeminization in humans.

Masculinization, Defeminization, and Bisexuality

Studies of sexual differentiation of reproductive anatomy have identified that two types of gonadal hormonal action are necessary, masculinization and defeminization, to produce male anatomy. Sexual differentiation of female reproductive anatomy doesn't appear to involve gonadal hormones reflecting that the sexually dimorphisms in anatomy are biased to form female phenotypes (Jost, 1970). This anatomical system was applied to behavioral sexual differentiation with masculinization resulting in display of male homotypical behavior (mounting-intromission, and ejaculation) and defeminization resulting in an inability to display female homotypical behavior (receptivity, lordosis in nonprimates). Studies demonstrated that masculinization and defeminization were separable processes that were independently expressed and could be affected by differences in the hormonal environment. The separability of these two processes made it possible to develop bisexuality. If a genetic male was masculinized by the hormonal environment, but not defeminized, he would exhibit bisexual behavior. Similarly, if a genetic female was exposed developmentally to a masculinizing hormonal environment, but one that did not defeminize her, then she would exhibit bisexuality. Some degree of bisexuality is common as described more fully below. Indeed, the only known species where males and females only express homotypical behavior (CIS males and CIS females, in current parlance) is the mythical Ramstergig (Beach, 1971). Bisexual behavior was sufficiently common that Young argued that female rodents were bisexual and males were not (Young, 1961b). Goy and Goldfoot (1975) found that there were species where females were not bisexual but the males of that species were. Furthermore, comparisons made across species revealed that one sex and only one sex exhibited bisexual behavior or bisexual potential (they just needed the appropriate sex-specific hormones administered; Goy & Goldfoot, 1975). In some species it was the female who showed bisexuality, while in others it was the male. No exception to this pattern of bisexuality has been reported in the 45 years since the publication of Goy & Goldfoot, 1975. Further evidence that this complementarity between bisexuality and CIS behavior comes from studies of inbred guinea pig strains 2 and 13. Gonadectomized and treated with the appropriate steroids, strain 2 males, but

not females were bisexual, while in strain 13 females were bisexual, but males were not. Thus, the pattern of bisexuality appears to be heritable and to have a genetic basis possibly reflecting the expression of masculinization and defeminization. If masculinization is over expressed, it might not be detected in males as that is the way in which males are made, but it could result in bisexual females who were not defeminized, but masculinized. The opposite pattern would be seen if defeminization was over expressed. The notion that the two processes underlying behavioral sexual differentiation might account for bisexuality is one that Goy found of great interest, but which was not further explored.

Socialization and Sex Differences in Social Behavior

When Goy went to the Primate Lab in Madison, WI, to learn primate juvenile behavior, he studied juvenile monkeys who had been reared under a paradigm considered "normal" (Harlow, 1965). In this rearing system monkeys were housed with their mothers in single cages for the first 30–60 days of life and then housed singly for the rest of their childhood after removal from their mothers. During the first year of life, juvenile monkeys were put together in small groups where 5 days/week; they received 30 min/day of social interaction with 4–5 male and female peers (Harlow, 1965). Monkeys reared this way did not show the aberrant behavior displayed by monkeys reared in total social isolation, and thus this became the standard laboratory infant rearing condition (Wallen, 1996). What was not apparent until more monkeys were reared in this peer-access condition was that male monkeys were severely developmentally affected by the limited access to peers. Harlow's view of the adequacy of the Primate Lab rearing conditions reflected his view that juvenile play was a sign of adequate socialization and peer-reared monkeys showed high levels of play. What they didn't show was juvenile foot-clasp mounts where the juvenile males (and sometimes females) mimic the adult males' copulatory mount. Peer-reared males rarely if ever show this mount. The rarity of foot-clasp mounts among peer-reared males is probably not, as previously suggested (Harlow, 1965; Harlow & Lauersdorf, 1974), a normal developmental pattern but instead is characteristic of a socially deficient rearing environment. Goy encountered this negative attitude in the discussion of a paper he had given on animal models of human sexuality (Goy & Goldfoot, 1975). Robert Rose, who worked with monkeys in semi-natural social groups, stated: "… monkeys should be studied in a natural setting; caged monkeys are crazy." In typical fashion "… Goy replied that 'crazy' is perhaps an exaggeration, and the term 'legally insane' is more accurate" (Goy & Goldfoot, 1975). Rearing conditions had a profound effect on juvenile behavior. So, Goy stopped using the Primate Lab rearing method and reared all subsequent subjects in a mother-peer rearing condition in which 4–5 mother-infant pairs were continuously housed together during the infant's first year of life and then weaned at 1 year of age and singly housed, with daily 30 min interactions with the other group members. The change in the rearing had a profound effect on the juvenile monkey's behavior. Mother-peer reared males showed high levels of play as well as foot-clasp

mounts. Interestingly, males and females did not differ in their threatening behavior, whereas when peer-reared there was a clear sex difference in threat, with males exhibiting four times the number of threats as did females. By contrast when the monkeys had continuous access to peers during their first year of life, males and females displayed an almost equal number of threats, with females displaying slightly more than did the males. Thus, rearing condition affected a variety of social behaviors and affected whether sex differences in social behavior were evident (Wallen, 1996; Wallen et al., 1981). What had started as a practical matter – why were our juvenile males not mounting – revealed the importance of behavior developing in a specific social context in order to see sex differences in juvenile behavior.

Timing of Androgen Exposure and Separation of Effects on Genitalia and Behavior

Probably one of Goy's most important papers is entitled *"Behavioral Masculinization Is Independent of Genital Masculinization in Prenatally Androgenized Female Rhesus Macaques."* When Goy published the lab's research showing that genetic female monkeys exposed fetally to androgens, either TP or DHTP, for long portions of pregnancy (50–75 days of gestation), their genitalia were masculinized as well as their juvenile behavior. Concerns were raised that because the treatment masculinized their genitals other monkeys might react to them as if they were males because they looked like males. While there is no reason to believe that monkeys have a notion of sex and that it is tied to how another monkey's genitals look, the possibility cannot be ruled out. The most direct way to address this issue is to find a prenatal treatment that modified the genitals, but does not modify behavior or modifies behavior, but does not modify the genitals. Goy et al. (1988) successfully found such treatments. They manipulated the timing and duration of treatment of pregnant females with TP. Treatments were either given early (first or second trimester) or late (third trimester). The duration of treatment was also varied so treatments were either 15 or 25 days. What did they find? Either 15- or 25-day early treatments masculinized genitals with female offspring of the longer treatment having more masculinized genitalia. Late treatments all occurred when genital differentiation was complete, so the had female-typical genitals and no masculinization for either short or long treatments. What about behavior? Two sexually dimorphic behaviors were collected, foot-clasp mounting (mounting) and rough and tumble play (play). Mounting was only increased by duration of treatment. 15-day TP treatments didn't increase mounting, whereas 25-day treatments either early or late did. Play was only increased by timing with early treatments not affecting mounting, but late treatment increasing play whether 15 or 25 days long. There was no consistent relationship between masculinization of genitals and masculinization of behavior. For mounting, two 25-day treatments increased mounting while one, 25-day Early treatment, masculinized both genitals and behavior, whereas the 25-day Late treatment masculinized behavior, but not genitalia. Thus, genital masculinization did not predict behavioral masculinization. A similar lack of relationship between anatomical

and behavioral masculinization was found for play, where only Late treatments masculinized play with both 15- and 25-day treatments doing so. Both of these treatments resulted in androgen exposed females having female genitalia. The Early treatments all had masculinized genitalia, but not masculinized play. Thus, for play there was no treatment that masculinized both play and genitalia. All treatments that masculinized genitals did not masculinize play. For mounting, the 25 day early treatment masculinized both genitals and mounting, whereas the late treatment didn't masculinize genitals but did masculinize mounts.

These results do not support the socialization explanation for masculinizing behavior as there was no consistent relationship between genital and behavioral masculinization. These results also highlight why identifying organizational effects of hormones is so difficult. There appear to be different periods of sensitivity to the masculinizing effects of TP but that sensitivity varies with the behavior measured. Secondly, it is suggested that anatomical masculinization and behavioral masculinization occur at roughly different epochs of pregnancy with anatomical masculinization generally earlier than behavioral masculinization, but this is not a strict dichotomy. This could explain why girls with congenital adrenal hyperplasia have masculinized genitals, but little masculinized behavior and no apparent effect on gender identity (Meyer-Bahlburg et al., 2004).

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