Sex is a concept that is divisible into genetic, gonadal, morphological, physiological, neural, and behavioral components. For example, the genetic sex of an individual mammal refers to its sex chromosome complement, that is, whether it has two X chromosomes, or one X and one Y chromosome. Gonadal sex refers to whether or not an individual has ovaries or testes. Behavioral sex refers to the display of male- or female-typical behaviors. In contrast to sex, sexuality is indivisible because, by definition, it refers to the unique composition of the various aspects of sex that identify the individual. An individual's sexuality is a mosaic of the components described above, as well as factors such as experience, socialization, partner preference, gender attributes, motivational state, performance capabilities, maturation, nutrition, and health. In addition, sexuality is the product of the evolutionary history of the species. Given that evolution depends upon inherited variation (the fabric of change) and environmentally regulated reproduction (the vehicle of change), as well as stochastic forces, how does an individual's sexuality develop? Answering this question requires that we study both ultimate and proximate mechanisms that determine sex and sexuality. In this chapter I outline experimental methodologies and theoretical approaches that may bring us closer to this goal.

Perspectives in biology and psychology often change with new discoveries. Usually this stimulates new research, but it can also limit our vision. This occurs when discoveries narrow our view of biological processes (Russert-Kramer 1989). It might be argued that our present understanding of the ultimate and proximate mechanisms underlying sexuality is an example of a perspective that has generated new data, but has also limited our vision.

Fifty years ago the prevailing view was that there were "male" (= androgens) and "female" (= estrogens) hormones that were responsible for "male" (= mounting and intromission) and "female" (= receptivity) sexual behaviors. The current view of sex differences in hormones and behavior can be traced to a paradigm shift that occurred 40 years ago. Phoenix and associates (1959) observed that exogenous testosterone propionate administered to pregnant guinea pigs will masculinize the behavior of female offspring. Their contribution was to show that the organizational effects of testosterone, which had been known to occur in the body, also occurred with regard to behavior, and by implication, the brain. This and subsequent work suggested that
sex steroid hormones early in development organize the body and the brain such that these same hormones later in adulthood activate sex-typical mating behaviors. Since that time a considerable literature on the sexual differentiation of the brain and behavior has accumulated apace with advances in technology.

Behavioral endocrinology has provided us with an ample collection of tools to address sexuality. The vast majority of these experimental designs and outcomes have been interpreted within the context of the organizational hypothesis. It can be argued that this perspective has limited our understanding of sexuality. Because the emphasis has focused on population characteristics, such as the mean lordosis quotient or mean number of mounts made by an animal, we have not progressed very far in understanding the behavior of the individual. I will try to turn attention from group means to sources of individual variation. Along the way I introduce some concepts to guide the reader as we explore new directions in the study of sexuality. This is followed by a collection of recent findings that I hope will shift our focus from current typologies and stimulate new ways of thinking. Implementation of finer-grain analyses, which take into account the context in which the behavior occurs, as well as the nature and pattern of hormone secretion, may bring us closer to our ultimate goal.

The chapter begins with a brief discussion of the meaning of sex, sexuality, phenotype, and phenotypic plasticity. I argue that sexual differentiation can be viewed as one type of phenotypic plasticity. This is followed by a discussion of some of the more widely held paradigms in behavioral endocrinology concerning sex and sexual differentiation. I point out how these paradigms fail to incorporate individual variation, phenotypic plasticity, and environmental effects on sexuality. The remainder of the chapter examines alternative model systems and paradigms that are useful in the study of individual variation in sexuality, and are divided into two main themes.

First, I discuss environmental organization of sex differences, and second, I discuss the evolution of the neuroendocrine mechanisms that control sex behavior. The first theme, environmental organization of sex differences in behavior, is discussed in three subsections. In the first subsection, I introduce species that can be particularly useful for elucidating the sources of individual variation leading to sexuality. One characteristic common to these species is that they exhibit sex differences that do not arise from sex chromosomes. Rather, sex differences in these species arise from environmental cues, such as ambient temperature and social cues from conspecifics. After these model systems are introduced, I illustrate how these species can be used to examine the mechanisms that lead to sex differences. For example, I evaluate the notion that differences in the size of specific brain areas can lead to sex differences in behavior. In the last subsection under Environmental Organization of Phenotypic
Plasticity, I present some examples of nongenetic effects on sexuality that are passed from generation to generation. This is followed by the second main theme of this chapter, which is concerned with the evolution of neuroendocrine mechanisms controlling sex behavior. I conclude with a theme that has been echoed throughout this book, that a thorough understanding of sex and sexuality requires a synthesis of knowledge, in this case from classic developmental biology and embryology, neuroscience, endocrinology, and particularly those fields that incorporate the environment and evolution such as ethology, comparative animal behavior, and evolutionary ecology.

Some Guiding Concepts

The individual, or more accurately, the unique constellation of genes that constitutes the individual, is the unit of selection in the broad scope of evolution. Thus, selection does not act at the level of definable traits, which may be adaptive; it acts at the level of the whole organism. The genotype refers to the allelic complement of the individual and does not change during the life of the organism. However, each genotype can lead to more than one phenotype. The phenotype reflects both the individual’s genotype, as well as the environment in which it develops, and thus the phenotype can change during the life span. This fact has become clear in the past decade as imaginative experiments in behavioral ecology and evolutionary biology have revealed the influence of life history and maturation on mate choice. Similarly, experiments in cellular and molecular biology have demonstrated that ontogenetic mechanisms constrain evolutionary change, particularly as they relate to the brain. Emerging from both areas has been the appreciation that the phenotype can change throughout different stages of an individual’s life history and that every genotype can yield a variety of phenotypes. Since evolution selects for outcomes, and not mechanisms, it is important that behavioral endocrinologists consider both individuals and context in both time and space as important elements in the development of sexuality.

Like sex, phenotype is a concept that describes the constellation of morphological, physiological, and behavioral traits that, when considered together, characterize the individual. Thus, the phenotype concept refers to aspects of an individual’s behavior, brain, body parts, physiology, or organs. Like the components of sex, these different phenotypic traits usually are concordant within time, space, and state of an individual, although this often has been a presumption without substantiation.

Phenotypic plasticity refers to the process by which the internal and external environments induce different phenotypes from a given genotype (McNamara and Houston 1996; Pigliucci 1996). The range of possible responses from an individual is
termed "the reaction norm." In natural populations, genetic variation in phenotypic plasticity is both trait- and environment-specific. The mechanisms underlying plasticity can be either committed and fixed, or labile and reversible. Sexual differentiation can be seen as a kind of phenotypic plasticity. For example, many vertebrate species lack sex chromosomes. In such species, gonadal sex can be fixed during embryonic development, as in the case of certain reptiles in which gonadal sex is plastic during a short period but is fixed by environmental temperature thereafter. In other cases, gonadal sex can change in adulthood, as in the case of certain coral reef fish in which gonadal sex is plastic and sex change is socially regulated in adulthood. Even in species with sex chromosomes, each individual possesses all of the genes necessary to develop the sexual phenotype of both sexes. These considerations together imply that the process of sexual differentiation represents a form of phenotypic plasticity.

Traditional Views in Behavioral Endocrinology Compared to the Study of Individual Variation in Sexuality

The individual emerges from the dynamic interactions within and across all levels of biological organization, from genes to molecules to cells to systems to organisms operating in environments both past and present. Thus, an individual's sexuality results from heritable traits, transmitted genomically or nongenomically, as well as environmental and social stimuli the individual experiences at different stages in its life history. Although behavioral endocrinology has revealed much about the proximate causes of sex differences in behavior, the prevailing hormonal organizational hypothesis of sexual differentiation is of limited value in the quest to understand sexuality.

The foremost reason is subtle but profound. Concepts become preconceptions when they narrow our perceptions, and the resulting orthodoxy thereby excludes alternative views, hypotheses, or preparations. Consider, for example, the "biological species concept" in evolutionary biology. Predicated as they are on sexual organisms, most species concepts are not readily applied to asexual organisms. Thus, the species concept excludes what can be learned about speciation from the study of asexual organisms. The same might be said of the hormonal organization hypothesis of sexual differentiation. While much has been learned about the physiology and, more recently, the molecular biology of sex determination and differentiation of the structures associated with sex in mammals, this information tells us little about the epigenetic process from which sexuality emerges. Genetic and gonadal sex are used to categorize individuals in a majority of vertebrates. These are generally discontinuous
and discrete traits; the individual has either the male chromosome complement or the female complement. In contrast, sexuality is a continuously variable suite of traits uniquely expressed in each individual. Because sexual reproduction requires the production of viable complementary gametes and the associated behavior to efficiently combine them, the system of sex determination is biased toward the production of the polar outcomes we refer to as male and female. In contrast, sexuality is more variable, producing both reproductive and nonreproductive phenotypes.

A second reason that the predominant behavioral endocrinology methods are of limited value is that we know only what we study, and we tend to study only what we know. In behavioral endocrinology, the majority of research is conducted on relatively few species, virtually all of them highly domesticated. This is particularly evident in studies of sex determination and sexual differentiation. In all of the preparations that have been studied in detail, sex chromosomes determine the type of gonad that will be formed. While this genetic difference facilitates the study of sex differences, it actually hinders our understanding of sexuality. That is, because genetic sex and gonadal sex are linked, it is difficult to distinguish epigenetic from genetic contributions to sexuality. Consider, for example, sociosexual behaviors displayed by both sexes, but at different frequencies or intensities. To what extent are the differences observed between adult males and females due to chromosomal constitution, differences in nongenomic yet heritable influences, maternal influences, the nature and pattern of gonadal steroid hormone secretion, or even sex-typical experiences?

Third, it must always be kept in mind that each individual is bipotential, arising as it does from a single cell. Even as adults both males and females are capable of displaying those behaviors characteristic of the opposite sex. The result is that the range of variation among individuals within a sex usually is greater than the difference between the averages for each of the sexes. In other words, although the sexes differ behaviorally in many ways, this difference is a statistical phenomenon. When trying to detect unifying principles it is often necessary to minimize individual differences. It is time to develop a set of approaches to studying individual differences that are as equally powerful as the mean-based approaches now used to reveal underlying principles.

Environmental Organization of Phenotypic Plasticity

Ideally, studies of the plasticity of the sexual phenotype would utilize animal models that exhibit sex-typical differences in the traits of interest, yet do not have the complications arising from sex chromosomes. In other words, a species that can illustrate
how different environments can elicit different phenotypes from a particular genotype without the confounding of sex-limited genes. Do such organisms exist in nature? In species with genotypic sex determination, such as mammals, the inheritance of specific chromosomes, whether in type or in number, fixes the sex of the individual at the moment of fertilization. Scientists have known for many years that in certain plants and invertebrates, the sex ratio is skewed and, further, that these deviations are due to environmental conditions. However, it has only been in the last two decades that we have come to realize that many vertebrates also exhibit environmental sex determination. There are two basic types, behavior-dependent and temperature dependent, and in both instances gonadal sex is determined after conception.

**Behavior-dependent Sex Determination**

In behavior-dependent sex determination, it is the individual’s perception of its social environment that establishes gonad type. Such species are sequentially hermaphroditic and exhibit one of three distinct patterns (Grober 1998). In protogyny, individuals mature and reproduce first as females and then, as they age, turn into males. In protandry, individuals develop and reproduce first as males, and then later turn into females. The third pattern is serial sex change in which the individual functions first as a female, changes into a functional male, and then reverts to female, repeating this process over and over again. This latter pattern is functionally equivalent to simultaneously hermaphroditic species in that individuals alternate their behavior and the type of gamete that is shed in successive matings. However, in alternating behavior-dependent sex determination, the gonads undergo a complete morphological change, producing exclusively the gonad-typical gamete during each successive phase, whereas in simultaneous hermaphroditism the gonads are ovotestes.

When sex change in coral reef fish was first discovered, the prevailing view was that the behavioral changes observed were a consequence of the changes in the gonads. Recently this idea has been turned on its head. In the bluehead wrasse, a single (type I) male dominates a coral head with the rest of the individuals being females or type II males. Within minutes of the dominant male’s removal, the largest female will begin to behave as a male, aggressively defending the coral head and soliciting other females. Morphological changes in the gonad are observed many days later and physiological changes are seen several days after that. In other words, it takes approximately 2 weeks after a new fish takes over before its gonads are transformed. Even if the largest bluehead female in a harem is ovariectomized, she will still exhibit all of these behavioral changes and, although muted, color changes following removal of the dominant male (Godwin et al. 1996). Indeed, even though these neutered females do not shed gametes, they entice other females to spawn with them. In most
instances this occurs immediately, as would occur when an intact female assumes the dominant role in the harem. Recent studies indicate that the transcript of the gene coding for arginine vasotocin changes in parallel with these behavioral changes (Godwin et al. 1998).

Temperature-Dependent Sex Determination

In many reptiles the temperature of the incubating egg determines an individual’s gonadal sex, a process known as temperature-dependent sex determination (TSD). Species with TSD lack sex chromosomes and have little or no genetic predisposition to respond to temperature in particular ways. For example, research with the red-eared slider turtle indicates that the physical stimulus of temperature is transduced in the midtrimester of development to modulate expression of the genes coding for steroidogenic enzymes and sex steroid hormone receptors (Crews 1996). This, in turn, alters the hormonal milieu, and the temperature-specific sex-determining cascades appropriate for that temperature stimulate and inhibit such that individuals develop as gonadal males or females. At intermediate incubation temperatures, hermaphrodites are not formed; rather the ratio of males to females changes relative to that of the higher and lower temperatures. Thus, in TSD species each individual has an equal ability to become a male or a female, and temperature serves as the trigger activating and suppressing the cascades that lead to the development of testes or ovaries. Environmental sex-determining mechanisms, of which TSD is one, are believed to be the evolutionary precursor to genotypic sex-determining mechanisms (Bull 1983; Janzen and Paukstis 1991).

Embryonic Temperature Shapes the Adult Phenotype

In the leopard gecko, incubation of eggs at 26°C produces only female hatchlings, whereas incubation at 30°C produces a female-biased sex ratio, and 32.5°C produces a male-biased sex ratio; incubation of 34° to 35°C again produces virtually all females. Hence, females from eggs incubated at 26°C are referred to as low-temperature females, whereas those females from eggs incubated at 34°C are referred to as high-temperature females; the two intermediate incubation temperatures are referred to as female-biased (30°C) and male-biased (32.5°C) temperatures.

By incubating eggs at these various temperatures and then following individuals as they age, we have found that incubation temperature accounts for much of the phenotypic variation seen among adults both between and within the sexes. For example, adult leopard geckos are sexually dimorphic, with males having open secretory pores anterior to the cloaca. In low-temperature females these pores are closed, whereas in females from a male-biased temperature they are open (Crews 1988). Head size is also
sexually dimorphic, with males having wider heads than females, yet within females, those from a male-biased temperature have wider heads than do those from a low temperature (Crews 1988). Similarly, although males are the larger sex, incubation temperature has a marked effect on growth within a sex. Females from a male-biased temperature grow faster and larger than do females from a female-biased temperature, and become as large as males from a female-biased temperature (Tousignant and Crews 1995).

Circulating concentrations of testosterone in both newborn and adult males are approximately 100 times higher than in adult females (Gutzke and Crews 1988; Tousignant and Crews 1995). However, the endocrine physiology of the adult varies in part due to the temperature experienced during incubation (Coomber et al. 1997; Tousignant et al. 1995). For example, plasma estrogen levels are significantly higher in males from a female-biased temperature than in males from a male-biased temperature. Among females, circulating estrogen levels are significantly higher, and androgen levels significantly lower, in low-temperature females than in females from a male-biased temperature. Whether this also is the case in hatchlings from different incubation temperatures is not yet known.

Incubation temperature also has a major influence on the nature and frequency of the behavior displayed by the adult leopard gecko. For example, females usually respond aggressively only if attacked, whereas males will posture and then attack other males but rarely females (Gutzke and Crews 1988; Flores et al. 1994). However, males from a female-biased temperature are less aggressive than males from the higher, male-biased temperature and, although not as aggressive as males from that same incubation temperature, females from a male-biased temperature are significantly more aggressive toward males than are females from a low or female-biased temperature. These same females show the male-typical pattern of offensive aggression. Incubation temperature also influences the ability of exogenous testosterone to restore aggression. Following ovariectomy and testosterone treatment, low-temperature females do not exhibit increased levels of aggression toward male stimulus animals, whereas females from male-biased temperatures return to the high levels exhibited while gonadally intact (Flores and Crews 1995). This suggests that incubation temperature influences how the individual responds to steroid hormones in adulthood.

Courtship is a male-typical behavior. In a sexual encounter, the male will slowly approach the female, touching the substrate or licking the air with his tongue. Males also have a characteristic tail vibration, creating a buzzing sound, when they detect a female. Intact females have never been observed to exhibit this tail-vibration behavior, regardless of their incubation temperature. However, if ovariectomized females from low and male-biased temperatures are treated with testosterone, they will begin
to tail-vibrate toward female, but not male, stimulus animals; males appear to regard such females as male because they are attacked (Flores and Crews 1995).

Attractiveness in the leopard gecko is a female-typical trait and is measured by the intensity of a sexually active male’s courtship behavior toward the female. Females from a male-biased temperature are less attractive than are females from lower incubation temperatures (Flores et al. 1994). Interestingly, attractiveness in high-temperature females is greater than that of females from male-biased temperatures and not different from that of low-temperature females. Long-term castrated males are attractive and initially courted by intact males, but on olfactory inspection they are attacked. This suggests that both sexes can produce both a female-typical attractiveness pheromone and a male-typical recognition pheromone as do red-sided garter snakes (Mason et al. 1989). As is the case with females, incubation temperature influences sensitivity to exogenous hormones in males. Estrogen treatment will induce receptive behavior in castrated males if they are incubated at a female-biased temperature, but not if they are incubated at a male-biased temperature.

The nature and pattern of an individual’s growth, hormone secretion, and behavior are expressions of brain activity. Thus, it is reasonable to expect that sex differences in growth hormone secretion and behavior arise from sex differences in the brain, that is, neural phenotypes (Balaban 1990, 1997; Bass 1996, 1998). It stands to reason, therefore, that the morphological, physiological, and behavioral phenotypes we have discovered in the leopard gecko might be the reflection of neural phenotypes. Much to our surprise, we discovered that there is no statistically significant sexual dimorphism in the preoptic area (POA) and ventromedial hypothalamus (VMH) between males and females at those incubation temperatures that produce both sexes (Coomber et al. 1997). However, there are consistent differences across incubation temperatures. For example, females from the male-biased incubation temperature have a larger POA than females from low and female-biased incubation temperatures. Further, the volume of the POA is larger in both males and females from the male-biased temperature than in animals from the female-biased temperature. Similarly, the volume of the VMH is larger in low-temperature females than in females from the male-biased temperature. These data suggest that the incubation temperature of the embryo may directly organize the brain independent of gonadal sex.

Metabolic activity in particular brain areas was measured using the cytochrome-c oxidase (COX) method. We found that males on average have greater COX activity in the POA, whereas females on average have greater COX activity in the VMH (Coomber et al. 1997). Again, incubation temperature is an important determinant, but so too is gonadal sex (i.e., hormones). Males and females from the male-biased temperature have greater COX activity in the POA than animals from the other
incubation temperatures, whereas females from the female-biased temperature have greater COX activity in the VMH than females from the male-biased temperature.

As mentioned, there is a significant increase in aggression in females with increasing incubation temperature (Flores et al. 1994). In reptiles, the nucleus sphericus and external amygdala are homologous to the medial and basolateral amygdala of mammals, respectively; as in mammals, both areas are involved in the control of aggression. Analysis of females from different incubation temperatures reveals that COX activity increases in this and other brain areas as a function of incubation temperature in a manner that parallels these differences in aggression within females.

Are these differences in the volume and COX activity of brain nuclei a consequence of a direct action of temperature, or an indirect result of temperature's sex-determining function? This has been tested using the classic gonadectomy and hormone replacement therapy approach (Crews et al. 1996a). As might be expected, androgen treatment following gonadectomy stimulates courtship behavior in both males and females, as well as in females from the all-female-producing temperature (Crews et al. 1996a; Flores and Crews 1995). Following gonadectomy, the volume of the POA decreases and that of the VMH increases in males as well as in females from the male-biased temperature, but not in females from the all-female-producing temperatures. Similarly, androgen treatment results in an increase in metabolic capacity in the POA and in the VMH in males and both types of females. In summary, androgen treatment increases courtship behavior and metabolic activity in the brain area controlling male-typical courtship behavior without a concordant increase in volume of this brain area. Thus, it is more likely that it is the activity, not the size, of a structure that is important for sex differences in behavior. This latter result is also similar to previous findings that females from different incubation temperatures have different behavioral sensitivities to exogenous testosterone (Flores and Crews 1995), which in other lizards reflects steroid hormone receptor abundance (Crews et al. 1996b; Young and Crews 1995). Thus, it appears that male and female geckos from the same incubation temperature respond to sex steroids in the same way, but that within a sex, geckos from different incubation temperatures respond to sex steroid hormone manipulation differently. These behavioral and neurobiological differences indicate that incubation temperature is the primary stimulus in the differentiation of the brain areas involved in sociosexual behaviors.

Although we do not know at this time if hormones differ in the yolk, during embryogenesis, or among same-sex neonates from different incubation temperatures, steroid hormones cannot explain the fact that the level and intensity of aggressive behavior is a function of incubation temperature, not gonadal hormones. Similarly, the rate of growth appears to be organized directly by temperature, perhaps via a
temperature effect on growth hormone secretion. Males grow faster and larger than females from the same incubation temperature. If estrogen is administered to eggs incubating at a male-producing temperature, the individual will be a female (rather than a male), yet its rate of growth will be accelerated. Finally, if ovariectomized at birth, low-temperature females grow at a rate characteristic of males from the male-biased temperature, whereas females from the male-biased temperature do not show an acceleration of growth or an increase in aggression (Tousignant and Crews 1995). Although prehatching organizational effects with a postnatal hormonal contribution could explain these results, such evidence suggests that incubation temperature plays an important role in determining an individual’s response to gonadectomy and hormone replacement therapy.

Cause vs. Consequence, Size vs. Activity

An important question in the study of brain-behavior relationships is whether brain differences predispose individuals to behave in a certain way, or if individual differences in behavior result in corresponding differences in the brain. This issue of cause vs. consequence is of critical importance in the interpretation of data on the size of sexually dimorphic areas in the brain. A dramatic example of sexual dimorphism in brain structure is found in some species of songbirds. The size of the brain areas involved in the production of song changes as a function of gonadal hormones and, further, individuals with more complex songs have larger and more complex song control brain nuclei (e.g., the higher vocal center or HVC) (Arnold 1992). Similarly, a number of investigations have established that the brain of male and female mammals can differ in a variety of ways, including the size of nuclei implicated in the control of sexual behavior. Do individuals having larger song nuclei learn more complex songs, or do individuals that learn large song repertoires develop large song nuclei?

To answer this question, Brenowitz et al. (1996) hand-reared marsh wrens and exposed them to one of two song repertoires having a fivefold difference in size. Although the two groups showed corresponding differences in the size of their learned song repertoires, they did not differ in the volume of the HVC or in the size, number, or density of neurons within this nucleus. These results suggest that the relationship between song complexity and brain space develops independently of early or later experience, either as a result of inherent differences among individuals in the size of song nuclei, or of other epigenetic influences such as individual differences in hormones in the yolk, steroid metabolism, or allocation of the type or quality of nutrition. In the last instance the nutritional status of the embryo and neonate (Nowicki et al. 1998) and perhaps even the presence of nonsteroidal estrogens in the
food (e.g., phytoestrogens or grain fungi) or xenobiotics resulting from industrial contamination must also be considered.

There are examples in which the size of a brain area and its metabolic activity are concordant. In sexual whiptail lizards, the anterior hypothalamus (AH)—POA is larger in males than in females, whereas the VMH, which controls female-typical receptivity, is larger in females (Crews et al. 1990). During hibernation or following castration, the AH-POA shrinks and the VMH enlarges (i.e., both brain areas become female-like); a similar relationship applies to the neurons within these areas (Wade and Crews 1992). These results indicate that in the ancestral sexual species structural dimorphisms develop in the adult and, further, that testicular androgens control the seasonal growth of these areas. Studies using metabolic markers of brain activity reveal that the AH-POA is more active in male, and the VMH more active in female, whiptails during mating (Rand and Crews 1994). The metabolic activity of brain nuclei can also vary according to uterine position. In gerbils, the sexually dimorphic area of the preoptic area (SDA-POA) is responsible for copulatory behavior in males (Yahr 1995) and, as females differ in their sexual behavior according to intrauterine position, the SDA-POA is likely to be involved in their behavior as well. Cytochrome oxidase histochemistry reveals long-term changes in the metabolic capacity in the SDA-POA, with 2M (located between two males) female fetuses having greater activity than 2F (located between two females) female fetuses (Jones et al. 1997). There also is a difference in COX activity in the posterior anterior hypothalamus, an area replete with neurons containing gonadotropin-releasing hormone (GnRH) (Silverman et al. 1994), which may explain the physiological differences between 2M and 2F females.

This relationship between the size of a structure and its activity is not universal, however. For example, because the unisexual whiptail displays both male-like and female-like pseudosexual behavior, it would seem reasonable to predict that its brain would also be bisexual, resembling both the male and the female of the ancestral sexual species. To my great surprise, the AH-POA and a VMH of the unisexual whiptail is not significantly different in size from those seen in females of the sexual ancestral species (Crews et al. 1990; Wade and Crews 1991). There also is no difference in neuron somata size in those individuals exhibiting male-like pseudosexual behavior compared with those exhibiting female-like pseudosexual behavior (Wade and Crews 1992). Even if the parthenogen is treated with androgen so that it exhibits only male-like behavior, the brain remains unchanged. The size of the AH-POA is not correlated with male- or female-like pseudosexual typical behavior. Another example is the red-sided garter snake. In this species only the males court. Despite the sex-
specificity of behavior, the AH-POA and the VMH are not dimorphic in area (Crews et al. 1993).

These findings raise questions as to the meaning of sexual dimorphisms in the vertebrate brain. For example, we hear today that homosexuals behave as they do because their brain is different from that of heterosexuals. However, the parthenogenetic lizard described above clearly retains the ability to express malelike behaviors, but not because it has a masculinized AH-POA. It retains the ability to express malelike behaviors because it has co-opted the progesterone surge to trigger the masculine behavioral potential that remains in a brain that is “feminized” with regard to the size of particular brain areas. In this case, “feminized” refers to a definition related to the size of these brain areas in the heterosexual species. In summary, behavioral differences need not be paralleled by structural differences in the brain.

The Importance of Experience and Age

Throughout the 1950s and 1960s ethologists, as well as comparative and physiological psychologists, were preoccupied with questions of the development of behavior and, in particular, the role of experience. Many experiments demonstrated that certain experiences during specific periods of development were critical to the formation of those behavioral suites characteristic of the species (e.g., displays typically performed by males during courtship) or of a sex (e.g., maternal behavior). For example, the young male white-crowned sparrow must hear his species song during a particular period of development if he is to sing in adulthood. In rats, rabbits, and monkeys, multiparous females are more skilled mothers than are nulliparous females (Lehrman 1962).

Experience is cumulative, depending upon preceding events and, at the same time, setting the stage for future experiences. Social deprivation, environmental complexity, and nourishment can alter the physiology and structure of the brain (Bhide and Bedi 1984; Kraemer et al. 1984; Turner and Greenough 1985). Although we have known for years that sociosexual experience and age influence an individual’s sexual behavior, there has been only limited work relating these effects to brain morphology and activity (e.g., see Keverne et al. 1993; Kollack-Walker and Newman 1997; Witkin 1994; Witkin and Romero 1995). Engaging in sexual behavior brings about a decrease in the size of the sexually dimorphic nucleus of the bulbocavernosus in the spinal cord of male rats (Breedlove 1997). In rhesus monkeys, rearing individuals without mothers or allowing only brief periods of interaction with peers results in elevated levels of aggression in males, and submissive behavior in females, in adulthood; if reared in same-sex vs. mixed-sex groups, males showed less of the male-typical foot-clasping mounting behavior as adults, whereas females exhibited more of this behavior.
as adults (Wallen 1996). Hormones can combine with the social environment early in life to shape adult sexuality. If a female zebra finch is treated with estrogen shortly after birth so as to masculinize its song control nuclei, and then reared with other females from adolescence to adulthood, it will prefer females as sex partners when given androgen in adulthood (Mansukhani et al. 1996).

Since organisms age as they gain sociosexual experience, but do not necessarily gain sociosexual experience as they age, it is important to separate the effects of age from those attributable to experience. For example, neuron density in the hippocampus decreases with age in humans, monkeys, and rats, but it is not clear to what extent epigenetic factors such as experiential or environmental factors could contribute to these age-related changes in the volume of the hippocampus. In rats, aging is associated with a decline in the density of synaptic input to GnRH neurons in the POA, but reproductive experience will counter this trend and maintain synaptic input to GnRH neurons at young adult levels (Witkin 1992; Witkin and Romero 1995).

To assess the relative effects of age and sociosexual experience, we incubated leopard gecko eggs at temperatures that produce either all females or a male-biased sex ratio (26°C or 32.5°C, respectively) and then raised the animals in isolation for at least 1 year before housing some lizards together in breeding groups. In this way it was possible to obtain animals that were either young (1 year of age) or old (2 to 3 years of age), as well as socially experienced or inexperienced.

Sociosexual experience and age can have different effects on the volume and COX activity of brain areas (Crews et al. 1997). For example, the volume of the POA increases with sexual experience in low-temperature females, but not in females from the male-biased temperature, whereas COX activity in the VMH increases in females from the male-biased temperature, but not in low-temperature females. In males as they age, the POA becomes smaller and more active. Such results indicate that the volume and metabolic capacity of specific brain regions are (1) dynamic in adulthood, changing as leopard geckos age and gain sociosexual experience, (2) that the size and activity of brain areas can be independent, and (3) the embryonic environment influences the nature and degree of these changes.

Hormonal Inheritance, Transgenerational Effects, and Individual Variation

Transmission of traits across generations occurs by the inheritance of genes, but characteristics can also be transmitted across generations by nongenomic means, such as culture in humans. Phenomena similar to cultural transmission have been described in animals, such as tits stealing cream from milk bottles in England, black rats feeding on pine nuts in Israel, and washing of rice by macaque monkeys in Japan.
Consider what is involved in genomic vs. nongenomic patterns of inheritance. The first involves individual-to-individual transmission, whereas the latter involves context-to-context transmission that, in turn, influences individuals. These contexts may derive from the culture or local population or from properties of physiological processes. Take, for example, stimuli experienced during fetal development. Forty years ago Christian and LeMunyan (1958) demonstrated that the stress of crowding on pregnant mice adversely affected the physiology and behavior of two generations of progeny. Similar stress effects can be induced by handling pregnant females or housing them in socially unstable conditions; the mechanism of action appears to be due to activation of adrenocortical responses of the mother and the consequent effects on fetal endocrine physiology (Herrenkohl 1979; Sachser and Kaiser 1996; Ward 1972; Ward and Weisz 1980). Moore (1995) and colleagues (Moore et al. 1997) discovered that mother rats behave differently toward male and female pups and, further, these differences reinforce and accentuate subsequent sex differences when the pup reaches adulthood.

Nongenomic inheritance can also occur as a consequence of the uterine environment during pregnancy. Among mammals that bear litters, the fetuses are arranged like peas in a pod, with flanking neighbors except for those at the ends. Clemens was the first to propose that the position of the female rat fetus in the uterus relative to its siblings influences its morphology, physiology, and behavior in adulthood (Clemens 1974; Clemens and Coniglio 1971). Evidence for the intruterine-position effect has now been found in rats, gerbils, mice, and even humans. One of the features of this phenomenon is that a 2M female is exposed to higher levels of androgen produced by the neighboring males than a 2F female (Clark et al. 1991). As adults these 2M females have lower estrogen and higher testosterone levels, have a masculinized phenotype, are less attractive to males and more aggressive to females, and produce litters with significantly greater male-biased sex ratios relative to 2F females (cf. Clark and Galef 1995; Vom Saal 1991).

Exposure to excessive hormone levels during pregnancy as a result of genetic or metabolic disorders, or hormone therapy of the mother, can lead to abnormal development of secondary and accessory sex characters, including psychosocial alterations in gender identity and gender role in adulthood (Reinisch et al. 1991). Hormonally induced organization also occurs normally in human beings. For example, the cochlea produces spontaneous otoacoustic emissions, with females producing more than males. This sexual dimorphism in emissions is not evident in the female of opposite-sex fraternal twins, suggesting that the prenatal environment created by the male fetus decreases these emissions in females with male co-twins (McFadden 1993; McFadden and Lochlin 1995; see also McFadden and Pasanen 1998). As will become
evident, it is not insignificant that otoacoustic emissions occur in lizards and turtles and are temperature-dependent in adults (Köppl 1995). The circulating levels of androgen and sex hormone-binding globulin during the mother’s pregnancy may also have an organizing effect on both the hormone profiles and psychosocial test scores of young adult women (Udry et al. 1995). In this remarkable study, a substantial portion of the variance in the women’s “gendered” behavior was accounted for by measurements of androgen exposure only during the midtrimester of development and by their circulating levels of androgen as adults.

Environmental conditions can also influence the psychosexual differentiation of embryos or neonates. Cooling newborn rats to 18°C (the normal temperature of the mother is 34°C) for 2 hours delays the testosterone surge that occurs normally about 2 hours after birth which, in turn, affects sexual behavior in adulthood (Roffi et al. 1987). Finally, in Siberian hamsters, as discussed extensively in chapter 7, the photoperiod experienced by the mother during pregnancy influences the circadian rhythms of the offspring (Stetson et al. 1989).

All of these examples indicate that environmental factors influence brain organization. Does a similar phenomenon occur in egg-laying vertebrates? The shelled egg is not immune from maternal or uterine influences (Crews and Bull 1987), and classic studies in embryology used chicken eggs to establish that steroid hormones influence the development of sexually dimorphic structures and behavior (reviewed in Adkins-Regan 1981, 1987; Shumacher and Balthazart 1985; Sayag et al. 1991). Like milk (Koldovsky 1980; Kacsoh et al. 1989), yolk is a significant repository of circulating hormones and reflects the hormonal profile of the mother at the time of its deposition. In fish, the circulating concentrations of a variety of steroid and other hormones in the female are greatest at the time the eggs are yolking and these hormones have an important impact on the development of the fry (Bern 1990; Schreck et al. 1991). In the Japanese quail, circulating steroid levels in the female are correlated with steroid levels in the yolk of eggs (Adkins-Regan et al. 1995).

In the zebra finch and the canary, the testosterone content in the yolk varies predictably across eggs within a clutch and these differences correlate with subsequent behavioral differences in the adults (Schwabl 1993; see also Schwabl et al. 1997). Eggs laid on later days have higher testosterone levels than eggs laid earlier which, in turn, correlates positively with the subsequent growth and social rank of the individual; that is, males hatched from eggs laid later tend to grow faster and achieve higher social status (Schwabl 1993, 1996b). As would be expected, circulating levels of testosterone, which increase during yolking, vary among females and under different environmental regimens (Schwabl 1996a). The spotted hyena displays similar, but more pronounced, maternal effects on offspring phenotype, as discussed in chapter 9.
In this species the female’s clitoris is hypertrophied, resembling the male’s penis. This unique pattern of female urogenital development results from maternal ovarian hormone production that is transformed and transported to the fetus by the placenta. Other aspects of the female’s phenotype, such as body size and aggressive behavior, are also masculinized such that females dominate males in the social group (Glickman et al. 1997). I have classified this process, in which the endocrine state of the mother influences the offspring via placental transfer or through hormones deposited in the egg yolk, as “hormonal inheritance” (Crews et al. 1989). Study of monotremes would be particularly important in this regard.

The Evolution of Neuroendocrine Mechanisms Controlling Sexual Behavior

Can evolutionary history be used as a lens to approach issues of molecular action in relation to reproductive behavior? Beginning with a chance observation 20 years ago (Crews and Fitzgerald 1980), we have made considerable progress toward this goal. Along the way, we have made some important discoveries that have been extended to mammals.

Because the ancestors of most animals are extinct, most approaches to the evolution of neuroendocrine mechanisms regulating behavior have yielded approximations. The whiptail lizards present a rare case in which representatives of both the ancestral sexual and the descendant unisexual species still exist, representing a “snapshot” of evolution and enabling study of the evolutionary process directly (Crews 1989). Further, because the parthenogenetic species exists only as females, yet still exhibits both malelike and female-like sexual behaviors, we are able to probe the fundamental nature of sexuality without the complication of gender (Crews 1988). Finally, they enable us to examine two fundamental issues in behavioral neuroscience from a new perspective: First, how might the cellular mechanisms that control sexual behaviors have evolved? Second, how do the neural circuits that subserve male-typical and female-typical sexual behaviors differ?

When considered together with the sex-changing fish, the experiments with the unisexual whiptail lizard make it clear that sexuality resides in the brain and not in the gonad. Individual unisexual whiptails show primarily female-like pseudosexual behavior during the preovulatory stage when 17β-estradiol (E2) concentrations are relatively high and progesterone levels are relatively low; just the opposite is seen during the display of malelike pseudocopulatory behavior in the postovulatory phase when concentrations of E2 are low and progesterone levels have increased. Androgens (either testosterone or dihydrotestosterone) are not detectable in the circulation of the parthenogen. Changes in behavior commonly occur at transitions in circulat-
ing levels of hormones, and the close parallel between the severalfold rise in proges-
terone levels at ovulation suggests that it may be the hormone responsible for the 
expression of pseudocopulatory behavior. Supporting evidence is that (1) subcuta-
neous implants of progesterone elicit pseudocopulatory behavior in ovarietomized 
parthenogens housed with ovarietomized, estrogen-treated parthenogens; (2) intra-
hypothalamic implantation of progesterone elicits mating behavior in castrated males 
of the sexual species; and (3) progesterone upregulates androgen receptor (AR) gene 
expression in the AH-POA.

Although the unisexual whiptail descended directly from a sexual whiptail, the two 
species differ in an important aspect of their reproductive biology; namely, circula-
ting concentrations of E$_2$ in reproductively active parthenogenetic whiptails are 
approximately fivefold lower than in reproductively active female sexual whiptails 
(Young and Crews 1995). Since changes in the circulating concentrations of sex 
steroid hormones can have dramatic effects on endocrine physiology and behavior, 
one might expect the severalfold difference in E$_2$ between the parthenogenetic whiptail 
and the sexual whiptail to be accompanied by species differences in estrogen-
dependent phenomena. This is evident in comparisons of ER messenger RNA 
(mRNA) content in the POA of unisexual whiptails and female whiptails. Thus, an 
inverse relationship exists between sex steroid receptor gene expression in the POA 
and circulating sex steroid hormone concentration. The increased level of ER gene 
expression in the POA may result in a greater sensitivity to the circulating concentra-
tions of E$_2$, which could in turn result in lower levels of E$_2$ through feedback effects.

Why is ER mRNA expression in the POA higher in the parthenogenetic whiptail 
than in its maternal ancestral species? One possibility is that it is linked to the 
increased gene dosage resulting from the triploid nature of the genome. It has been 
suggested that one reason that polyploid species differ physiologically and eco-
logically from their diploid relatives is that the increased gene dosage may result in 
higher enzyme and hormone levels. This phenomenon has been well documented for 
a number of enzymes in several plant species. Allozyme analysis of a number of 
diploid and polyploid whiptail lizards, including the parthenogenetic whiptail, demon-
strate that each of the three sets of chromosomes are actively transcribing genes at 
rates proportional to the gene dosage, rather than one chromosome set becoming 
inactivated, as might be expected. Triploidy, therefore, could result in increased sen-
sitivity to E$_2$, not only by increasing the basal rate of ER production but also by 
increasing estrogen-dependent gene transcription rates as the target gene number is 
also increased.

Consistent with this hypothesis, the species differences in circulating concentrations 
in E$_2$ and ER mRNA are accompanied by differences in sensitivity to E$_2$. Dose-
response studies reveal that lower dosages of estradiol benzoate are required to induce receptive behavior, as well as changes in gene expression, in the VMH of parthenogenetic whiptails compared with sexual whiptails. As in other vertebrates, the VMH is involved in the hormonal induction of receptive behavior in whiptail lizards (Wade and Crews 1991; Kendrick et al. 1995). Thus, species differences in reproductive physiology (e.g., brief follicular phases, as in the rat and mouse, compared to extended follicular phases, as in whiptail lizards and rabbits) may explain species differences in neuroendocrine controlling mechanisms. Thus, at least three factors may contribute to species differences in endocrine physiology and behavior: (1) sensitivity to sex steroid hormones, (2) hormone-dependent regulation of sex steroid hormone receptor gene expression, and (3) neuroanatomical distribution of steroid receptor gene expression, especially in nonlimbic structures.

How could an androgen-dependent male-typical mating behavior of the sexual ancestral species evolve to become a progesterone-dependent malelike pseudosexual behavior in the unisexual descendant species? The courtship behavior in males of the sexual ancestral species depends upon testicular androgens. Gould and Vrba (1982) pointed out that existing features can be produced by two distinct historical processes. One of these is adaptation, or the gradual selection of traits resulting in improved functions. Some traits, however, evolved from features that served other roles, or had no function at all, and were co-opted for their current role because they enhanced current fitness. This latter process may be termed exaptation. In adaptation, traits are constructed by selection for their present functions, while exaptations are co-opted for a new use.

Evolution depends upon individual variation; without it there would be no basis on which to evolve. This question is of biomedical importance because individual variation in response to standardized stimuli is fundamental and affects every aspect of healthcare. How does this relate to the whiptail lizards?

Some males of the sexual ancestral species are sensitive to progesterone; that is, in about one third of castrated males, administration of exogenous progesterone restores the complete repertoire of male-typical sexual behavior. Progesterone is probably exerting its stimulatory action as a progestagen and not via conversion to other sex steroid hormones. Other data suggest that progesterone acts via the PR and not via the AR. Thus, in the sexual ancestral species, individual variation in sensitivity to progesterone appears to have served as the substrate for the evolution of the novel hormone-brain-behavior relationship observed in the parthenogen. That is, the elevation of progesterone following ovulation presented a reliable stimulus that, given the low circulating concentrations of androgens, was co-opted to trigger mounting behavior in the parthenogen.
Is this behavioral responsiveness to progestin in males specific only to reptiles? What little is known of the physiology of progesterone in males points to a functional role. For example, $17\alpha, 20\beta$-dihydroxyprogesterone stimulates spawning behavior in castrated rainbow trout (Mayer et al. 1994). In male rats there is a pronounced diurnal rhythm in progesterone secretion, with the peak in progesterone levels coinciding with the period of greatest copulatory activity (Kalra and Kalra 1977). When administered in physiological dosages (rather than the pharmacological dosages usually used) progesterone causes some castrated male rats to mate with receptive females; when combined with subthreshold dosages of testosterone, all of the males respond (Witt et al. 1994, 1995). Further, this progesterone response is blocked by the progesterone antagonist RU486. Finally, recent experiments with transgenic mice indicate that males with a null mutation for the PR not only exhibit deficits in sexual behavior while intact, but also have a severely impaired capacity for maintaining sexual behavior following castration (Phelps et al. 1998). Thus, although progesterone has long been thought of as a "female" hormone involved in the control of female-typical sexual behavior, this evidence points to a previously unsuspected role of progesterone in the control of male sexual behavior.

Concluding Remarks

Variation results from the inherited genotype, environmental context, and the interaction between genotype and environment. Traditionally separate, molecular and developmental biologists and ecological and evolutionary biologists have recently focused on the epigenetic properties of the genotype-environment interaction. This is the well-traveled domain of psychobiology. Psychobiology offers a bridge between perspectives by recognizing that two levels exist in the organization of the adult sexual phenotype. Primary organization is the process of sexual differentiation that follows the determination of the gonad and is manifest as the morphological, physiological, behavioral, and neural traits that characterize the sexual phenotype. Secondary organization follows and is the basis of an individual's sexuality. Sexuality results from heritable genetic variation as well as nongenomic factors that include, but are not limited to, sex steroid hormones. Some of the other factors include (1) the environments encountered throughout life, (2) age and sociosexual experiences, and (3) the psychological and physiological condition of the mother.

This conceptual separation of the mechanisms that determine gonadal and morphological sex from those that shape sexuality is central to any study of individual differences. However, in species in which gonadal sex is determined at fertilization by sex chromosomes, primary and secondary organization are linked, thereby becoming
a confounding variable in studies of reproductive traits and sexuality. Thus, assessing
the relative contributions of genetic and environmental influences requires alternative
animal model systems in which the determination of gonadal sex is independent of
 genetic sex. Such a comparative approach generates new ideas about cause vs. con-
sequence and size vs. activity in brain-behavior relationships, the importance of
experience and age, and how hormonal inheritance, transgenerational effects, and
individual variation are interrelated. With such information it becomes possible to
study directly the evolution of the neuroendocrine mechanisms that control sexual
behavior.

Because individual variation is the substance of evolutionary change, understand-
ing its organization will require both new paradigms as well as alternative animal
model systems that allow separation of the effects of genes and hormones from
environmental and experiential stimuli. In general, much of the research on the
proximate mechanisms underlying the establishment of the sexual phenotype has
emphasized the role of gonadal sex hormones in the development of sexual dimor-
phisms. But it is time to refocus, move away from differences in mean values of males
and females, and instead direct our attention to the individual variations within each
sex. The diverse natural systems described herein suggest that factors other than sex
chromosomes and the steroid hormones secreted following gonadal differentiation
can play important roles in the development of within-sex differences in sexual
behavior. Some possible factors discussed include (1) embryonic environment (broadly
defined to include not only the hormones produced by neighboring fetuses or found
in the yolk but also physical factors such as temperature or number and type of other
conspecifics), (2) the psychological and physiological condition of the mother during
pregnancy or egg-laying, (3) the sociosexual experiences during growth and adult-
hood, and (4) the aging process.

Along this line, it might be more profitable to view hormones and other factors
during embryogenesis as allowing for the growth of neural connections, whereas
participation in particular behaviors throughout life specifies and consolidates the
unique functional integrity of the attendant neuroendocrine systems of each individ-
ual (Crews 1987). For example, an individual’s sociosexual experience not only can
modify its mating behavior, but experience also can change how it responds to sex
steroid hormones. In guinea pigs, the amount of sexual activity experienced as a
juvenile affects the level of sexual behavior displayed as an adult, as well as modifies
the individual’s response to castration and androgen replacement therapy (Valenstein
and Young 1955). In cats, males that have had sexual experience before castration
persist in displaying sexual behavior, whereas males that are sexually naive prior to
castration show an abrupt cessation in sexual behavior; conversely, castrated, sexu-
ally naive male cats given exogenous testosterone take longer to exhibit sexual behavior than castrates that have had sexual experience (Rosenblatt 1965). In gulls, testosterone treatment of males reared in social groups induces sexual behaviors, but not in males reared in isolation; males reared in social groups until sexually mature and then subjected to social isolation for 2 weeks exhibit lower levels of sexual behavior in response to exogenous testosterone than similarly reared males exposed to unfamiliar conspecifics (Groothuis 1995).

One interpretation of these data is that sociosexual experience mediates the effects of androgen by affecting the individual’s sensitivity to androgen, perhaps by influencing receptor density, the metabolism of the hormone, or alterations of neural circuitry, or a combination of these. Consistent with this hypothesis is the observation that the behavior of the partner can regulate the abundance of steroid receptor in the brain independently of the gonads (Hartman and Crews 1996). Thus, experience can have a permanent organizing effect on behavior and, hence, the brain. Lehrman (1962) noted that “the two sexes within the same species might differ with respect to the relative degree of dependence of their sexual behavior upon the presence of various hormones and upon various situation and experiential factors” (p. 142). This same logic can be extended to individual differences. The leopard gecko illustrates how such nongenetic factors can affect the differentiation of the adult phenotype without the confounding of genetically based sex differences. In this species, incubation temperature accounts for much of the variation in morphology, endocrine physiology, sociosexual behavior, and the size and metabolic activity of associated brain areas.

A final question is whether the relationship between individual differences in levels and intensity of sociosexual behavior is the cause or consequence of individual differences in relevant brain areas. Experience is continuous, punctuated by discrete events that shape subsequent behaviors. Recent studies suggest that the behavior, or the predisposition to behave, appears to be a consequence of brain activity, rather than the behavior causing the differences in brain activity.

Related to this issue is the finding that it is not the size, but the activity, of a brain area that matters. It may be then that differences are more likely to be reflected in the regulation of genes encoding receptor expression, metabolic activity, hormonal modulation of sensory processing, and so forth, rather than in neuronal circuitry, distribution of receptors, or the volume of brain areas. This has important implications for how we approach the problem of brain-behavior causality. How and why individuals differ is perhaps the original question in both psychology and biology. The ideas presented herein are not novel, and can be found in the writings of D. O. Hebb, Z. Y. Kuo, D. S. Lehrman, and C. H. Waddington. The plasticity of the sex-
ual phenotype and how each individual emerges out of its own unique circumstances will require integrating classic developmental, ethological, and neuroscience concepts with more current perspectives. By exploiting preparations provided in nature and developing new approaches, the foundation for a paradigm shift leading to a better understanding of individual differences will be laid in much the same way that it was for sex differences four decades ago.

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