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# Understanding the Bases of Sex Differences

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In very simple biological systems, reproduction can be accomplished by a single individual. In more complex systems, reproduction requires the interaction of two individuals differing from each other with respect to what we call sex. Dimorphism of sexual phenotype, function, recognition, and behavior reflects a sequence of remarkable evolutionary adaptations that have occurred over time. The diversity of biological adaptation is exemplified by the reproductive mechanisms of different species, ranging from spontaneous to reflex ovulation and from external to internal fertilization. The pairing of gametes from two individuals also allows natural selection to proceed at a pace and in directions keyed to environmental cues as well as to mutational events.

To understand the specifics of male-female differences, let us consider the two sexes as accommodating each other for reproductive efficiency. One sex, the female, periodically sheds one or more of a finite number of gametes (ova). These ovulations are the products of a series of integrated events that occur in the ovary and synchronize the sexual process in the female. Thus, only for a brief period do sexual receptivity, the availability of a fertile ovum, and the proper uterine or tubal environment coexist. Whereas the male's reproductive pattern could also be periodic, such a system would require that sperm shedding, copulatory behavior, and the aggression necessary to fend off competitors be keyed to the cycles of a receptive female, a coincidence that would be difficult to accomplish. An alternative system, the usual one, has the male constantly producing fertile gametes and sexually ready. Thus, the male produces an unlimited number of sperm, which bud off from stem cells lining the spermatic tubules of the testis. While this system is wasteful of gametes, the other aspects, such as aggression, can be useful for other life chores. In the seasonal breeding species, both males and females can practice reproductive economy in the off-season.

The functional-anatomic arrangement of endocrine and gametogenic cells is different in the two sexes. The ovary's endocrine function and the ovulatory mechanism are anatomically associated to each other. The developing follicle is on a suicide mission that will furnish a discharged and exhausted remnant (the corpus albicans) after its individual oocyte's life history is decided. In contrast, the spermatozoa are formed within tubules by a process that requires testosterone production by an extratubular compartment, the stroma with its Leydig cells. The gonads of each sex also show considerable biosynthetic and secretory differences; the primary secretory products of the ovary are estrogens and progestins, whereas the major secretory products of the testis are androgens. In either sex, cyclic (female) or tonic (male) gonadal secretions cause structural and behavioral changes that mirror endocrine function. Some of these are markers of sexual receptivity (such as sex skin in primates) or reproductive competence (for example, as in the case of the cock's comb). In all species there are major overlaps between the sexes, and the addition of complex and highly variable social factors in humans often obscures the exact mechanisms of events.

The articles in this issue summarize the factors surrounding sex differences with respect to ontogeny, phenotype, and hormone-sensitive actions. They follow a sequence that begins with genetic sex differences and carries through to cell, tissue, organ and, finally, systemic effects of gender. Gordon and Ruddle (page 1265) describe and explain the current understanding of sex differences in genes and chromosomes. The X and Y chromosomes cause the sexing of the gonad. The transfer of sex-determining information from genes to the gonadal precursors results in the formation of either ovary or testis. Haseltine and Ohno (page 1272) discuss these gene products and the mechanism by which these products define the gonads. A plausible case is made for the ingenious scheme (*1*) requiring that sex differences are specified by a small number of genes acting to cause gonadal differentiation, the gonadal products thereafter being responsible for the more widespread and contemporary aspects of structural development and function in the body.

After gonadal determination, fetal-neonatal endocrine function takes over, organizing the internal and external genitalia along male or female lines. The way that this happens was envisioned by Alfred Jost (*2*). Dual genital development occurs up to the point of gonadal secretion. The absence of the testis allows completion of the female internal and external genitalia. The testis causes the arrest of female internal genital development and drives the completion of the masculine internal ducts as well as perineal closure and fashioning of the male external genitalia. Later, gonadal secretions determine genital structure and function in the adult. Wilson, George, and Griffin (page 1278) describe the sequential development of the internal and external genitalia. These principles and the specifics of target tissue steroid metabolism have become central to our understanding of mechanisms of steroid hormone action. Bardin and Catterall

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(page 1285) carry this further as they review the role of androgens in the development and maintenance of many "male" target organs. These data underline the utility of (i) a widespread system of specific intracellular receptors for androgens and (ii) active end-organ metabolism of steroid hormones that is reflected in secondary sex characteristics. They stress the influence of sex steroids on constitutive proteins (enzymes) throughout the body, further extending the domain of sex even into processes such as carbohydrate metabolism.

In some species, gonadal androgen secretion at a critical period of intrauterine or neonatal life differentiates central nervous system mechanisms (such as gonadotropin control and sexual behavior) in a manner that complements the constant endocrine function of the testis. MacLusky and Naftolin (page 1294) review the sexual differentiation of the brain and point out the importance of brain metabolism of androgens to form estrogens. These sex-differentiating effects of sex steroids can also determine sexual behavior in the adult. McEwen (page 1303) carries this forward as he reviews the biological basis of sexual behavior in the adult.

Similarities between the patterns of neuronal concentration of androgens and estrogens are emphasized, thus implying a difference in hormone availability or postbinding events in the expression of male or female sexual behavior.

The scheme of a sexually dimorphic universe seems thus far to have fallen neatly into place. A small number of genes signals the gonadal differentiation of a small number of cells to form a sex-specific gonad. The message of sex is then amplified as the gonad begins to function by secreting specific products that cause differentiation along male-female lines (organization). The organized tissues, however, retain the ability to respond to sex hormones. This response (activation) further sustains and amplifies the genetic message in the mature sexually competent female or male individual. So far, so good.

In humans differences between the sexes in gender identity, behavior, sexual orientation, cognitive function, and gonadotropin regulation are often seen. The origin of these differences, especially the role of prenatal hormonal organization, remains in question. The evidence for both social and biological influence is strong. There are few experiments that have permitted other than outcome analysis, usually some time after development. Ehrhardt and Meyer-Bahlburg (page 1312) review this important area and analyze the available data from clinical material. The administration of hormones to pregnant women and studies on abnormal subjects without developmental treatments show a poor correlation between prenatal exposure to exogenously administered sex hormones and later activational events. But the picture is very complicated because the subsequent performance reflects the endocrine milieu which filled the interim and could have influenced the test situation. Their article indicates that, where found, effects of prenatal exposure to sex steroids results in a situation compatible with animal data. While this may be reassuring to clinicians concerned about possible misadventures of gestational therapy, it does not reveal much about the mechanism of action of prenatal hormones. The role of prenatal hormones in organizing human central nervous system function demands further investigation.

In the last article, Rubin, Reinisch, and Haskett (page 1318) review evidence for the hormonally activated aspects of sexually dimorphic behavior in humans. Again, problems in the gathering and interpretation of data have been encountered. In general, the studies, though extensive, deal with extreme cases and may not be definitive. The difficulties of establishing appropriate controls are impressive and social factors obscure the picture.

Despite shortcomings in clinical studies, it is now well recognized that sex differences are programmed from the beginning of ontogeny, are needed for reproduction, and have many consequences not directly related to fertility. We are fortunate that these times have afforded the support, technical developments, and intellectual climate necessary to produce the studies described in this series.

**References**

1. S. Ohno, *Major Sex-Determining Genes* (Springer-Verlag, New York, 1979).
2. A. Jost, *Recent Prog. Horm. Res.* **8**, 379 (1953).