The Requirements for Sexual Reproduction

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Summary. Sexual reproduction requires controls for gonadogenesis, genital differentiation, and sexuality. The initiating event is induction of testicular differentiation by an effect of the H-Y locus or a combination of X- and Y-borne genes. This paper reviews the evidence that testosterone, either directly or via regulated conversion to other steroids, controls sexuality as it does male genital differentiation. The point is also stressed that, despite their difference, sexual reproduction and individual homeostasis are intimately linked.

An overview of human sexual differentiation should begin with a consideration of the requirements for sexual reproduction. For this process, the first requirement is gonadogenesis: the development of organs with a capacity for gametogenesis and for hormone production. We have known for many years that the human gonad begins as a bipotential structure, capable of either ovarian or testicular differentiation, to which the germ cells migrate. Joso has been working actively on the sequence of testicular morphogenesis and has shown that the initial event is emergence of the Sertoli cell, following which the seminiferous tubules are organized. But what initiates the process? Ohno and Wachtel have proposed that the principal control is the H-Y antigen encoded under the direction of a locus on the short arm of the Y chromosome.

The second requirement of sexual reproduction is appropriate genital anatomy: a set of ducts and external genitalia adequate to convey the gametes to each other and subsequently to get the fertilized egg to a site for implantation and for growth of the fetus. Our knowledge in this area is better developed: two principal substances are involved, both arise in the fetal testes, and their actions are sequential but not necessarily cooperative. To Josso we are indebted for work on the secretion and action of anti-Müllerian hormone, and to Wilson for research on the roles of testosterone and dihydrotestosterone in Wolffian and external genital differentiation.

Finally, sexual reproduction entails a set of behavioral changes and, to a degree, subjective reactions, which we call sexuality. Gender identity denotes one's self-image as a member of one or the other sex. In fact, this identity has been assumed to be the reflection of the way one has been treated during infancy. The social sex, or sex of rearing, is determined by an instant's inspection of the external genitalia, and the signals conveyed to a largely non-verbal infant are said to imprint the gender identity. Now, though, the ontogenesis of this self-image is being rethought. Imperato-McGinley suggests that testosterone, either during fetal life or in the neonatal period, may orient the brain toward a male self-image.

Sexual arousal denotes the ability to respond to erotic stimuli: in the male, with erection; in the female, with vaginal lubrication and increased genital vascularity. Sexual appetite, sometimes termed libido, and its relation to initiation of sexual activities is a further facet of sexuality: in the human, we have traditionally attributed sexual urge to the male and to testosterone. Whether this view is more culturally than physiologically determined, we do not know. Finally, successful sexual reproduction requires a secure heterosexual object choice, lest arousal and libido lead only to ineffective reproductive performance.

Beyond the requirements for sexual reproduction lie the relationships between the physiology of reproduction and other aspects of physiology. All of physiology except reproductive physiology is bound inextricably to survival of the individual and is subject to evolutionary selection within that framework. By contrast, reproductive physiology is unique in that its purpose is the preservation of the species, not of the individual. Among the special attributes of reproductive physiology are a) an inherent (rather than epiphenomenal) sex dimorphism; b) major longitudinal change in activity during the life of the individual; and c) the requirement for a second individual for full expression. In view of the striking and pervasive differences between homeostatic and reproductive systems, it is interesting to examine the linkages between them that are reflected in many areas.

For instance, although the H-Y antigen appears to be the signal to testicular differentiation, it is also a histocompatibility factor. In other words, this single gene locus contributes to two of the most powerful differentiating attributes of individuals: male versus female; self versus other. Beyond the scope of this discussion, a histocompatibility role of H-Y has been observed in renal transplant programs, and sex differences in immune response and autoimmune diseases are, of course, well-known.

The glycoprotein hormones include the three gonadotropins (follicle-stimulating hormone, luteinizing hormone, and chorionic gonadotropin) as well as thyroid-stimulating hormone. The A chain of the dimeric hormones is identical for all four glycoproteins, whereas the B chain is immunologically and biologically distinct. Why should thyroid stimulation be evolutionarily linked in this way to the hormones that control gonadal function?

Although androgen and estrogen are produced in the adrenal, the amounts are too small to substitute for gonadal secretion. As we know, the synthesis of all steroids begins with acetate and cholesterol. The hormone aldosterone is required principally for the regulation of mineral balance, that is, the defense of extracellular sodium concentration and thus volume.

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and for the regulation of extracellular potassium. The many functions of cortisol, the principal glucocorticoid, include protection of the blood glucose level, sensitization of blood vessels to catecholamines, protection against inflammation, and reaction to stress of all kinds. Finally, the roles of the sex steroids are well-known. What is the evolutionary advantage of linking hormones required from minute to minute (aldosterone) and day to day (cortisol) with those whose function is over a generation to generation time span (sex steroids)?

Testosterone turns out to be the central compound in the regulation of many aspects of sexual reproduction: it is the key compound in internal duct differentiation and the precursor for the steroid responsible for external genital differentiation in the male; new evidence shows that it is actively secreted for the first four months of life, although the significance of this period of secretion, great as it may be, is not yet known. But, further, testosterone is responsible for non-sexual aspects of puberty. It is a principal stimulus to growth in the pubertal male; it ultimately arrests growth by closing the epiphyses; and it is responsible for both development and maintenance of muscle strength and athletic prowess in the adult male. We tend to separate these features from sexual significance per se. Are we wrong? Are these features of the male principally sexual in their significance?

The strategic role of testosterone is noteworthy. It is active on its own, controlling Wolffian development, the pubertal growth spurt, epiphyseal closure, and certain aspects of secondary sexual development. It is converted by target tissues to the reduced metabolite dihydrotestosterone, a step occurring in at least the testis, urogenital ridge, skin, brain, prostate and liver. (The fact that dihydrotestosterone is synthesized within the target tissue makes plasma levels difficult to interpret.) Testosterone is also metabolized by a branching pathway to etiocholanolone, an inactive compound, and androsterone, a weak androgen. This pathway is of no known importance but is, interestingly, thyroxine-dependent.

Finally, the obligatory synthesis of estrogen via androgen, and the fact that both sexes make the same hormones, puts testosterone squarely at the center of endocrine sexual differentiation. Indeed, the differences in male and female secondary sex characteristics can be viewed as the result of two regulatory decisions: how much androgen to make, and how much of it to convert to estrogen. In rough approximation, these questions can be answered as follows for testosterone and estradiol:

<table>
<thead>
<tr>
<th></th>
<th>Daily testosterone synthesis</th>
<th>% Conversion to estradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis</td>
<td>6,000 mcg</td>
<td>0.25</td>
</tr>
<tr>
<td>Ovary</td>
<td>300 mcg</td>
<td>50.00</td>
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</table>

Conclusions

Consideration of the above remarks on sexual differentiation suggests some unresolved issues, the first of which is, in part, semantic.

Should there be another designation than "antigen" for H-Y antigen? Although that term reflects the historical development of knowledge of the gene, it does not express the action of the protein; as others have asked, why is not this antigen antigenic? Why is it not inactivated by an antibody? Indeed, could sex determination be controlled by the ability in the female to inactivate the antigen and the inability of the male to do so?

Where does the H-Y antigen operate? We have pointed out that Jost's studies indicate that the earliest evidence of testicular differentiation is the appearance of Sertoli cells and that these cells presumably help to orient and thereafter construct the seminiferous tubules. Do the Sertoli cells have the two H-Y anchorage sites? How is the appearance of Sertoli cells evoked and their function stimulated?

What are the quantitative determinants of H-Y expression? Several papers have shown higher levels of H-Y antigen in YY males, suggesting that the locus is constitutive. H-Y positive XX males and XX true hermaphrodites show H-Y antigen levels seemingly intermediate between the normal female and the normal male. Are these values different from those of the normal male? Perhaps some of the new assays will help to answer these questions.

How is the phenotype determined in mosaic individuals? If the H-Y antigen is soluble, and if, in the felicitous phrase of Ohno, XX cells can be "enticed," why is this hegemony not complete?

What signal controls ovarian differentiation? Is it the indifferent, that is, nonterritorial, fate of the bipotential gonad? Is there an inherent tendency of the primitive gonads to differentiate along female lines, as is true for the internal and external genitalia and for certain other systems? Or, rather, is there an "ovary-inducing antigen"? As a corollary, what can be learned from the ovarian suicide in Turner's syndrome? We know that 45,X individuals have oocytes early in their fetal and even postnatal development, but these disappear early. In essence, the Turner's patient does not have menses principally because she has the menopause before she can achieve a menarche. Are there lessons in this phenomenon than can illuminate the normal menopause?

What accounts for the persistence of the uterus and tubes (Müllerian structures) in true hermaphrodites and in patients with mixed gonadal dysgenesis? True, occasionally there is a vas deferens on the side of the testis, but uterine suppression rarely occurs in these patients, although it does in the cryptorchid male with one severely defective testis. Is anti-Müllerian hormone deficient in both true hermaphroditism and mixed gonadal dysgenesis?

Why is there no Wolffian development in patients severely masculinized by congenital adrenal hyperplasia? Is this purely a matter of dosage, timing, and localization of testosterone production, or does anti-Müllerian hormone play a role in preparing for testosterone?

What is the relationship between the phenotype and receptor status in the varieties of male pseudohermaphroditism? Wilson has begun to delineate variants of androgen insensitivity, but there remain patients with apparently identical phenotypes but with striking differences in androgen binding and processing.

Finally, the phenomenon of sexual differentiation, so far, is unique in its dependence on end-organ processing of arriving hormones. Intracellular receptors and enzymes are critical in determining abnormal versus normal phenotypes. Does variation in such controls within the normal range play a role in determining individual differences in phenotype? Could varia-

1 This value varies during the menstrual cycle.