A question of Y?

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Sex Determination, Differentiation and Intersexuality in Placental Mammals. By R. H. F. Hunter. Cambridge University Press: 1995. Pp. 310. £50, \$79.

In *The Genetical Theory of Natural Selection*, published in 1930, R. A. Fisher suggested that the difference between the sexes might depend on a single Mendelian factor that switches on one or other possible alternative. Admittedly, males and females in both humans and the fruitfly *Drosophila melanogaster* differ not just in one gene but in a whole chromosome, but it seemed that the sex of platyfish might be determined by a single gene. Because sex in *Drosophila* is primarily determined by the number of X chromosomes, the chance of finding such a gene in this species was rather remote. But the discovery that in humans and other mammals the Y chromosome is closely associated with males once again opened the possibility of finding the sex-determining gene, which was named *TDF* for testis-determining factor in humans, and *Tdy* in the mouse.

The name reflects the idea publicized by Alfred Jost that male development requires hormones produced by the fetal testis, whereas female development happens automatically in the absence of these hormones. Intense research during the past 20 years has resulted in proposals of several candidate genes for *TDF*. Following the announcement that the insertion of a small piece of DNA containing the murine homologous gene into genetically female XX mouse embryos is successful in inducing male development in some of them, the *SRY* gene is today widely accepted as the testis-determining gene.

This book provides a clear and factual account of the experimental evidence that has led to the present position, against a background of normal and abnormal sexual development. It contains ten self-contained chapters, from "Historical landmarks in studies of reproduction and sex determination" to "Concluding thoughts and a current perspective", and although fully referenced, the book is very readable. My one criticism is the absence of scale bars from some of the illustrations.

Ronald Hunter is a reproductive biologist specializing in farm animals, his species of choice being the pig. Pigs produce many eggs at ovulation and often show abnormalities of sexual development, such as the presence of ovotestes or of an ovary on one side and a testis on the other. These animals, which are a source of financial loss, are classified as 'inter-sexes', whereas the same abnormality in humans would be referred to as 'true hermaphroditism'. The difference in terminology

reflects the fact that the biology of domestic animals is seen in the context of that of simpler organisms, in which 'hermaphroditism' implies the ability of individuals to produce both functional eggs and sperm. By contrast, fertility is not a requirement for gender assignment in humans, and the clinical term 'true hermaphroditism' is applied to individuals with testicular and ovarian tissue, neither of which is reproductively competent. In this respect, mouse terminology follows the human practice.

Most intersex pigs are genetic females, with two X chromosomes and apparently no Y-chromosomal material; nevertheless,

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Mixed blessing — a hermaphrodite, as depicted in an erotic mural from Pompeii.

some exhibit the aggressive behaviour of boars, indicating that although the testicular tissue lacks germ cells, testosterone secretion takes place and affects behaviour. To explain the masculinization, a 'downstream' mutation has been invoked, but it is less easy to account for the common finding of unilaterality, with an ovary on the left side and an ovotestis on the right side.

A similar intersexual condition is found in 'polled', or hornless, goats. The P gene causes hornlessness when in single dose, whereas in double dose it also causes testicular development in genetic females.

Probably the most famous intersex is the bovine freemartin, which many decades ago helped to lay the foundation of the hormonal theory of sex differentiation. A freemartin is a sterile heifer born as co-twin to a male calf. During gestation, the ovaries of the female fetus lose their germ cells and sometimes develop into testicular structures. About 80 years ago, Frank Lillie noticed that freemartins are formed only if the twins share a common circulation

owing to the formation of vascular anastomoses between the two fetuses, and he postulated that humoral factors passing from the male to the female twin cause the latter's intersexual development. The reason the female becomes masculinized, whereas the male does not become feminized, Lillie suggested, is that sexual differentiation occurs earlier in the male than in the female.

Freemartins are rarely found in other species such as sheep and goats, and the condition seems to be absent in primates. In human pregnancies with opposite-sexed twins, the female twin develops normally.

Nevertheless, humans have their fair share of sexual abnormalities, and some of these have provided the basis of our knowledge of sex determination. The discovery that men with Klinefelter's syndrome have XXY sex chromosomes, whereas women with Turner's syndrome have a single X and no Y, has led to the appreciation that the Y chromosome is involved in the determination of male sex, and various deletions of the Y chromosome have provided information on the location of genes for sex determination (*SRY*) and for fertility. But there are a few males who lack Y chromosomal genes and a few females with an intact Y chromosomes. To explain these exceptional individuals, the effects of genes on other chromosomes are invoked.

In mice, several genetic causes are known that give rise to XY females, one of them resulting from crosses between wild mice of the *domesticus* substrain with the inbred laboratory strain C57BL/6J. When the *domesticus* Y chromosome finds itself in the company of the chromosomes of this strain, it is incapable of inducing the development of normal testes, apparently because its testis-determining gene (*Sry*) acts too late and is forestalled by ovarian development. But what causes the delay? Recent evidence suggests that this gene is already transcribed in the embryos immediately after fertilization, when male embryos are already further advanced than female ones. Is there a connection between these findings, and what is their relevance to the process of sex determination? Also, in this day and age, should not more active consideration be given to the positive steps involved in the formation of the ovary, rather than regarding it as the result of a default pathway?

Hunter sets out the relevant facts and hypotheses in a perfectly detached manner, allowing readers to make up their own minds. The book is eminently suitable for the advanced students for whom it is intended, and is a must for their teachers, as well as for anyone involved in the field of mammalian sex differentiation. □

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