A POSSIBLE COMMON MODE OF ORIGIN OF HUMAN XX HERMAPHRODITES, 'Y-NEGATIVE' XX MALES AND XY FEMALES WITH NORMAL Y CHROMOSOMES

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UNLIKE most human 'XX' males, who contain a small but specific segment of Y-chromosomal DNA, XX true hermaphrodites (and a minority of XX males) are uniformly negative for Y-specific DNA probes[1]. The origin of such individuals has therefore been described as enigmatic[2]. I suggest here one possible mechanism of their origin within the framework of the hypothesis that X chromosome inactivation is a sex-determining device[3,4].

DNA analysis has validated the hypothesis[5] that most XX males originate through improper recombination between X and Y chromosomes such that the X acquires the male-determining sequences of the Y. The mechanism suggested here for hermaphrodites and 'Y-negative' XX males is essentially analogous, but with unequal recombination occurring in the female, between X chromosomes.

In the proposed mechanism (see figure 1) which depends on recent results[1] identifying a putative male-determining locus (*Tdf*) on the Y as well as the X, n is the copy number of the regulatory sequence(s) controlling *Tdf* activity. Due to rare unequal recombination, X chromosomes with a higher than normal copy number of such regulatory sequences might arise. For the sake of simplicity, these will be referred to as X^+ chromosomes. Such recombination might involve the *Tdf* exons as well, but we consider this to be a much less frequent event. The reciprocal product would be an X chromosome with less than n copies of the regulatory sequence (X^-). Two types of egg (X^+ and X^-) and four types of zygote (X^+X, X^-X, X^+Y and X^-Y) are then possible. If more than n copies of the regulatory sequence lead to an increased output of the testis-determining substance, X^+X individuals might develop into XX males; such males would type Y-negative. However, in a few X^+X embryos, because of random X inactivation, gonadal primordia would be expected to be composed predominantly or exclusively of cells in which X^+ is inactive [$(X^+)X$]. This would happen by chance alone. Such gonads would develop into ovaries and such females might transmit the X^+ chromosome if this higher than n copy number does not cause infertility. Other X^+X individuals may develop both ovarian and testicular tissue if the appropriate foci in the indifferent gonad become populated by $(X^+)X$ and $X^+(X)$ cells respectively. One would then expect the occasional occurrence of 'Y-negative' XX males and XX hermaphrodites in the same sibship. Such a family has been reported[6].

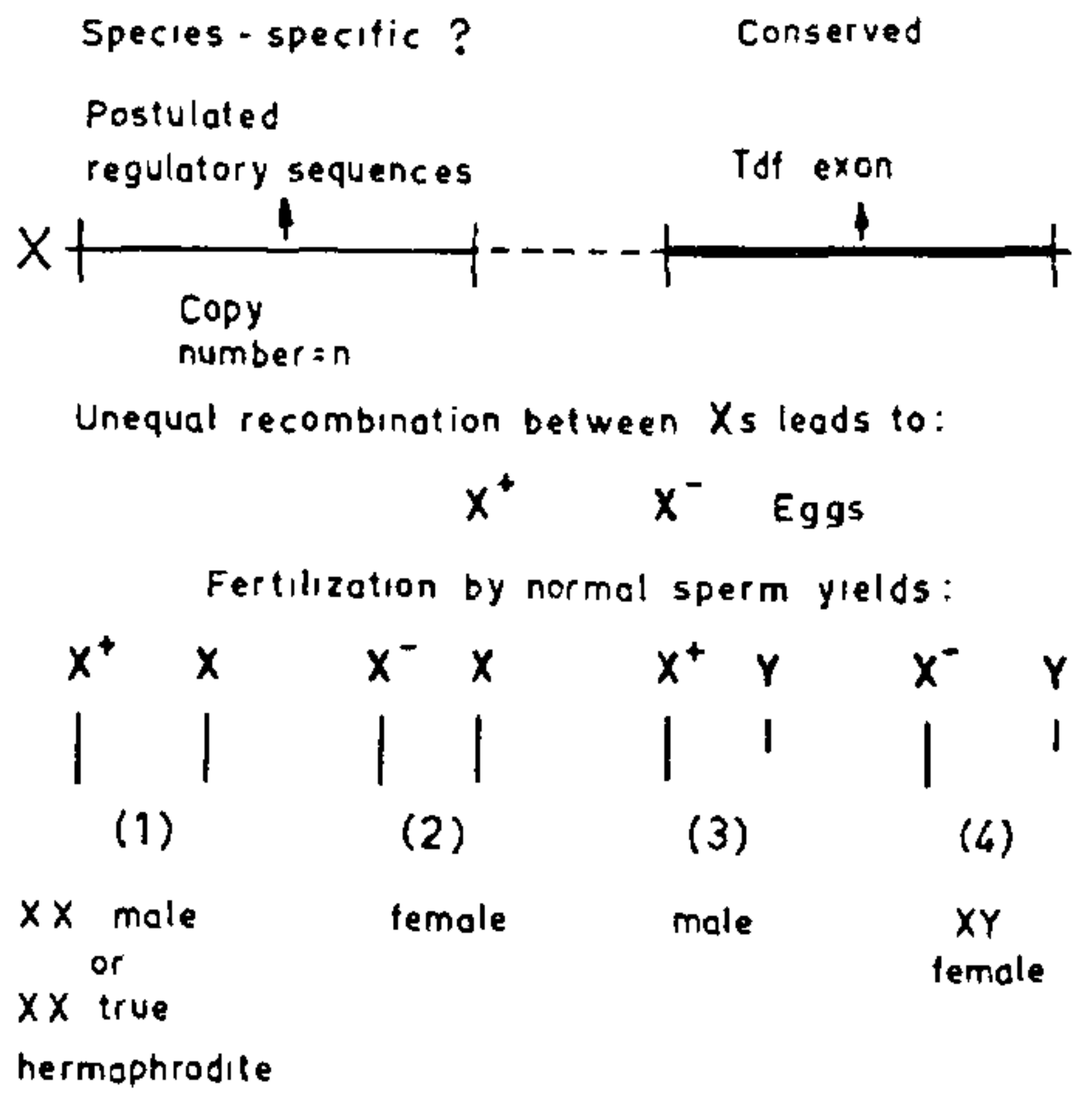

Figure 1. Unequal recombination between X chromosomes and subsequent X inactivation as possible causes of certain types of anomalous sexual development.

The copy number (n) of the regulatory sequence(s) may range from one to many. It is not implied that the location of the regulatory sequences relative to the *Tdf* exon is necessarily as indicated.

The X^+Y genotype would presumably develop into a 'normal' male. Transmission of 'Y-negative' XX maleness might then occur if such individuals are fertile and if recombination between the X^+ and Y in such males does not restore the copy number of the regulatory sequences to n or, if it is a multicopy sequence, a value close to n. Two sibs, an XX male and an XX hermaphrodite, both negative for Y probes, have been described (case 9, ref. 6). In such instances, additional molecular data might help distinguish between this hypothesis and others. Very rare cases of XO maleness may also be explicable on this basis (X^+O). An XO male whose X is maternal in origin and who is negative for Y-specific probes has been described[7].

Some XY females have a deletion of interval 1A2 of the short arm of the Y chromosome[1]. In other XY females no such Y deletion is demonstrable[1]. An X^-Y zygote might develop into a female who would

type positive for probes from interval 1A2. The rarity of the postulated unequal recombination and the infertility of X^-Y females make it unlikely that XY gonadal dysgenesis and XX males (or hermaphrodites) would occur together among related individuals. This may be a reason why such families are not known.

X^-X females might not transmit the X^- chromosome because they, like X^-Y females, might be infertile.

Others have suggested that XX hermaphrodites and XX males might arise due to a shifting of *Tdf* to a region of the X that escapes inactivation[1-8]. The suggestion has also been made that dosage effects of the kind discussed here and earlier[3,4 9,10], might involve an entire 'gonad differentiation locus'[8].

Regulatory sequences controlling the activity of *Tdf* are likely to be species-specific, and unlikely to be found among the highly conserved sequences in interval 1A2. This argument is based on a point of view developed by Mayr[11], and supported among others by recent work on sex chromosome-linked genes in butterflies[12], that at the heart of species identity are species-specific differences in sex chromosome-linked regulatory genes concerned with sex determination and reproduction. If this view is correct, it may complicate attempts to test the function of structural genes in interval 1A2 in transgenic mice.

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1. Page, D. C. *et al.*, *Cell*, 1987, **51,** 1091.
2. *New Scientist*, 1987, **116,** 29.
3. Chandra, H. S., *Proc. Natl. Acad. Sci. USA*, 1985, **82,** 6947.
4. Chandra, H. S., *Nature* (*London*), 1986, **319,** 18.
5. Ferguson-Smith, M. A., *Lancet*, 1966, **2,** 475.
6. Petit, C., de la Chapelle, A., Levilliers, J., Castillo, S., Noel, B. and Weissenbach, J., *Cell*, 1987, **49,** 595.
7. de la Chapelle, A., Page, D. C., Brown, L., Kashi, U., Parvinen, T. and Tippett, P. A., *Am. J. Hum. Genet.*, 1986, **38,** 330.
8. German, J., *Am. J. Hum. Genet.*, 1988, (in press).
9. *X inactivation and sex determination*, Talk in Workshop on X-inactivation, 7th Int. Congr. Hum. Genet., September 1986, Berlin.
10. *Sex determination viewed as a gene copy-number problem*, Talk in CCMB Symposium: The Frontiers of Tomorrow in Biology, November 1987, Hyderabad.
11. Mayr, E., *Population, species and evolution*, Harvard Univ. Press, Cambridge, USA, 1970.
12. Grula, J. W. and Taylor, O. R., *Evolution*, 1980, **34,** 688.

ALTERED NUCLEASE AND PROTEASE ACTIVITY IN CYANOPHAGE LPP-1 INFECTED CYANOBACTERIA *PHORMIDIUM UNCINATUM* AND *PLECTONEMA BORYANUM*

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THE interaction of cyanophage with its host is modulated by various factors including enzymes of metabolic pathways, especially the nucleases and proteases. Cyanophage infection is supposed to be dependent upon the host cellular components[1-3]. Cyanobacteria have very low level of nucleic acid degrading enzymes[4] which increases drastically after phage infection until complete lysis occurs[5]. An increase in the DNase activity after cyanophage infection probably plays a key role in the breakdown of the host DNA and the resulting products are quickly reincorporated into newly synthesized phage DNA[6,7]. Similarly, it has been shown earlier that host protein synthesis ceases immediately after infection with cyanophage followed by an enhanced synthesis of phage protein[6,7]. Cyanophage infection may also affect the proteolytic activity of the host to meet the demand for amino acids from the preformed sources. However, such studies are confined to only *Escherichia coli*-T phage system[8]. The present study was aimed at determining the eventual changes in the activity of nucleases and proteases in cyanophage LPP-1 infected non-heterocystous cyanobacteria *P. uncinatum* and *P. boryanum* under light and dark conditions.

Pure cultures of *P. uncinatum* (CU 1462/7) and *P. boryanum* (IU 590) and cyanophage LPP-1 were obtained through the courtesy of Dr R. S. Safferman, National Environmental Protection Agency, Cincinnati, Ohio, USA. Cultures were maintained in modified Chu 10 medium containing trace elements as described earlier[2,3] at $26 \pm 2°C$ in an illuminated culture room fitted with fluorescent light at an intensity of 480 ergs/cm^2/s. Lysate of LPP-1 cyanophage was obtained by infecting batch cultures of the cyanobacteria (6.5×10^6 cells/ml) with the