SEX DETERMINATION IN HUMAN

Joe Hin Tjio and **Albert Levan** (1956) discovered a better way to prepare chromosomes for viewing. This improved technique led to a strikingly clear demonstration of metaphase stages showing that 46 was indeed the human diploid number. Later that same year, C. E. Ford and John L. Hamerton, also working with testicular tissue, confirmed this finding.

Brief note:

(1)Since the X0 genotype in human beings is a female (having Turner syndrome), it seems reasonable to conclude that the Y chromosome is male determining in human beings.

(2)The fact that persons with Klinefelter syndrome (XXY, XXXY, XXXXY) are all male, and XXX XXXX, and other multiple-X karyotypes are all female, verifies this idea.

(3)A testis-determining factor (**TDF**), located on the Y chromosome that acts as a sex switch to initiate male development.

(4)During the **first month of embryonic development**, the **gonads** that develop are neither testes nor ovaries, but instead are indeterminate. At about **six or seven weeks of development**, the indeterminate gonads become either ovaries or testes.

(5)An antigen exists (Ernst Eichwald,1950s) on the surface of male cells that is not found on female cells. This protein was called the **histocompatibility Y antigen (H-Y antigen).** The gene for this protein was found on the Y chromosome, near the centromere.

(6)**David Page** (at the Whitehead Institute for Biomedical Research,) found twenty XX males who had a small piece of the short arm of the Y chromosome attached to one of their X chromosomes.

He found six XY females in whom the Y chromosome was missing the same small piece at the end of its short arm. This region, which did not contain the HYA gene, must **carry the testis-determining factor**.

(7)The first candidate gene from this region believed to code for the testis-determining factor was named the **ZFY** (Zinc Finger Protein Y-Linked) **gene**, for zinc finger on the Y chromosome. Zinc fingers are protein configurations known to interact with DNA. Thus, researchers believed that the ZFY gene, coding for the testis-determining factor, worked by directly interacting with DNA.

(8)Men **who lack the ZFY gene** have been found, suggesting that the testis-determining factor is very close to, but not, the ZFY gene.

[ZFY gene controls the initiation of sperm cell development, **but not maleness**.]

(9)Robin Lovell-Badge and Peter Goodfellow (1991) and their colleagues in England isolated a gene called **Sex-determining region Y (SRY)**—Sry in mice—*adjacent to the ZFY gene*. Sry has been positively identified as the testis-determining factor because, when injected into normal (XX) female mice, it caused them to develop as males . Although these XX males are sterile, they appear as normal males in every other way

Note also that the mouse and human systems are very similar genetically-**Justify.**

(i)The homologous the human SRY gene does not convert XX female mice into males.

(ii) *Like the ZFY gene product, Sry protein (the protein the SRY gene produces) also binds to DNA*.

(iii)The Sry protein appears to bind to at least two genes**.**

(iv)**One, the p450 aromatase gene (CYP19)** [Autosome linked, located on chromosome 15], has a protein product that converts the male hormone testosterone to the female hormone estradiol; the Sry protein inhibits production of p450 aromatase.

(v)**The second gene** the Sry protein affects is the **gene for the Müllerian-inhibiting substance**, which induces testicular development and the digression of female reproductive ducts.

(vi)The Sry protein enhances this gene's activity. Thus, the *Sry protein points an indifferent embryo toward maleness and the maintenance of testosterone production.* The sex switch initiates a developmental sequence involving numerous genes. **Eva Eicher** and **Linda Washburn** have developed a model in which two pathways of coordinated gene action help determine sex, one pathway for each sex.