In general, the mammalian male is heterogametic (XY) and the female is homogametic (XX). The mechanism of normal sex determination by means of XX-XY alternatives, therefore, forms the genetic basis for the developmental processes which transform a fertilized egg into either a female or a male.

A zygote of either XX or XY constitution transforms itself, within six to seven weeks after fertilization, into an embryo which morphologically, is neutral. The embryo possesses gonads which consist of 2 parts: an external layer of tissue, the cortex, characteristic of an ovary, and also an internal mass, the medulla, characteristic of the testis.
It is only after the neutral stage of development of the sexual rudiments that the genetic sex constitution of the embryo begins to exert a visible differentiation effect. In an embryo whose cells are with \(XX\) chromosomes, the cortical part of the gonad develops greatly, while the medullary part becomes inconspicuous. In other words, the neutral gonad is transformed into an ovary. In an embryo whose cells are with \(XY\) chromosomes, the reverse happens, the medullary part of the gonad enlarges and differentiates, while the cortical part disappears except for the remnants and the neutral gonad develops into a testis. This is the normal course of sex differentiation. But there arise many questions viz., What is the function of \(Y\) chromosome?. Why the 2 \(X\) chromosomes are needed for the normal female sex differentiation?. How the sex is differentiated in individuals with abnormal sex chromosome complements?.

The review of literature on the sex chromosome anomalies in human beings reveals that whatever the number of \(X\) chromosome may be, the presence of a single \(Y\) chromosome makes the phenotype of an individual as male. Thus, \(Y\) appears to be a strongly male determining chromosome and the basis of sex determination is an interaction between the \(X\) and \(Y\) chromosomes. This in fact contrasts with the
situation in Drosophila where the Y chromosome is required only for the production of the functional spermatozoa.

Hamerton (1971) has explained the role of a Y chromosome by citing a number of examples—such as X0 condition in certain mammals, the XX males and XY females in human beings, the sterile XX male pseudo-hermaphrodites in the domestic goat (Capra hircus) and a variety of intersexual conditions in human beings.

It is well known that if the Y chromosome is present, the gonads will be testes and in its absence the result is usually an ovary. Various cases reported with X0/XY mosaicism show that if the gonadal tissue contains a Y chromosome, it will differentiate into testes. Starkman and Robert (1967) reported that for differentiation of testes, there must be a sufficient number of cells with a Y chromosome in the gonads. Russell et al. (1964) found an identical ratio of XY/X0 cells, but showing an asymmetrical gonadal development. One gonad was a testis histologically and the other a streak.

Further, in human beings with 46 chromosomes, X0 females are almost invariably sterile girls with ovarian dysgenesis, short stature and often other somatic anomalies. It has generally been seen that the gonads are just streaks and lack germ cells. Hamerton (1965), however, has reported
that up to the third month of gestation, the 45, XO foetuses have relatively normal gonads containing germ cells similar to 46, XX gonads. After this, the germ cells begin to degenerate and the ovarian stromal tissue increases in the 45, XO relative to 46, XX ovaries. Thus, it appears that during the early stages of embryogenesis, a single X is sufficient for the development of ovaries. The presence of a single X chromosome does not prevent the formation and migration of the primordial germ cells into the germinal ridge, nor does it prevent the organization of the germinal ridge into an ovary. The loss of one X chromosome does, however, prevent the later development of a normal ovary. It is, therefore, clear that for the complete differentiation of the gonad into an ovary, 2 X's are needed. Secondly, even if the individual contains a single X unlike Drosophila, it won't have the phenotype of a male unless the Y chromosome is present, and the XO individuals are, in general, phenotypically females. Thus, the sex determination in man is independent of the ratio of X chromosomes to the autosomes. On the other hand, it is very much effected by the presence or absence of the Y chromosome.
Autosomal Genes and Sex-Determination

It is well known that in mammals certain autosomal genes can affect both the developmental pathways taken by the indifferent gonads and the formation of germ cells. In mouse, the \( W(WW \ WJ) \) series of alleles cause sterility in both the sexes and affect the number of germ cells but not the type of gonad (Mintz, 1957). In \( W^JW^J \) and \( WW \) mice, very few germ cells ever reach the gonadal ridge, but despite this a testis is formed in the male and an ovary in the female. This is a good evidence that the primary act of sex decision is at the somatic and not the gonial level.

In the goat (\textit{Capra hircus}), the autosomal dominant gene, controlling horn growth (polled \( P \)) also has a large number of pleiotropic effects in the homozygous state\((PP)\). Homozygous \((PP)\) genetic females are sterile polled male pseudohermaphrodites with testes which lack germ cells at birth but otherwise function normally and secrete normal levels of testosterone. The same gene which may cause sterility in some homozygous males as a result of epididymal occlusion also affect the litter size and sex ratio.

In homozygous \((PP)\) intersex goat foetuses, the germ
cells have been observed in relatively normal numbers in the testes after about 63 days gestation. By 126 days the germ cells are still present, but a greater proportion is in the process of degeneration and by the time of birth, all of them have disappeared. This is a conclusive evidence for the somatic nature of sex determination, because in this species we are dealing with a gene, which in genetic females, causes testicular development despite the presence of a XX sex chromosome complement and XX germ cells. The germ cells are formed and migrate to the germinal ridge. Despite this genotype, the gonads formed are the testes.

In human beings it has been suggested that 46, XX males are either mixoploids (46, XX/47, XXY) in which the XXY cell line has not been detected or they originated from 47, XXY zygotes, in which the Y chromosome was lost after sex decision. Alternatively the translocation of the Y borne male determining genes on to the X chromosome might have occurred. Neither of these suggestions seems really convincing and a similar but rare autosomal modifier leading to the testicular development and hence a masculine phenotype seems more reasonable. Such a modifier with variable penetrance and expressivity could also account for 46, XX male pseudohermaphrodites.
The other conditions of interest in man are pure gonadal dysgenesis with XX or XY sex chromosomes and testicular feminization in which there is a 46, XY chromosome complement associated with a female phenotype and testicular development. This condition is probably but not certainly caused by the action of a sex limited autosomal dominant gene which makes the target organs insensitive to the action of testosterone.

The data available clearly shows that (1) the act of sex decision simply depends on whether the indifferent gonads develop into a testis or an ovary (2) this act is mediated through the somatic elements of the gonial ridge and not the gonia (3) normally a Y chromosome is necessary for the development of a testis but under the influence of certain autosomal modifier genes, a testis can be formed in the presence of two X chromosomes and no Y chromosome and (4) only one X is necessary for the determination of an ovary, although the second X is necessary for its normal development.

Keeping all these facts in mind, Hamerton (1971) has suggested the following hypotheses which seem to be most substantiative in sex differentiation of the mammals,
particularly the human beings.

1. The act of sex decision is the stimulation of the primary sex cords of the medulla of the indifferent gonad to develop into a testis. In the female, the medulla regresses allowing the secondary sex cords of the cortex to develop into an ovary.

2. In the female, only one X chromosome is necessary for the cortical development which must, therefore, carry both the genes for cortical stimulation and its operator.

3. In the male, the Y chromosome or some part of it, acts as a controlling centre for the gene controlling the stimulation of the medulla or its operator. The operator genes are situated elsewhere in the complement than on the Y itself. In the presence of the Y chromosome or perhaps the short arm of the Y, these become activated and stimulate the medulla. The stimulation of the medulla inhibits development of the cortex.

4. Autosomal modifiers such as 'P' in the goat, and other forms including man act in a similar way to the Y controlling centre by activating the gene controlling medullary stimulation.

5. The most likely site for the gene for medullary stimulation and that for cortical stimulation is on the
X chromosome. This was originally suggested by Polani (1962) and more recently by McFeely et al. (1967). It should be remembered that the heteromorphic XY pair seen in the modern mammals has evolved from a homomorphic pair presumably carrying homologous genetic material and furthermore, that the two genes are likely to be situated in fairly close proximity, particularly if the activity of one leads to the suppression of the other.

6. As it is known, only one X chromosome is necessary for ovarian formation and migration of germ cells and it is suggested that the second heterochromatic X acts as a regulator of ovarian development and in particular regulates the rate of germ cell atresia. In normal ovaries germ cell atresia is a continuous process throughout gestation and post-natal life and only a small proportion of the gonia remains to form eggs. In the 45, XO state atresia is complete, so that no germ cells survive to puberty. The second X may also regulate estrogen production by the ovary, and abnormalities in this pathway may result in reduced amounts of estrogen and hence sexual infantilism. The abnormalities in somatic development seen so often in 45, XO females may result from abnormal rates of development which would normally be controlled by the second heterochromatic X.
7. It has been seen that XX germ cells cannot survive beyond birth in a testicular environment even when this is also XX. This may be owing to the wrong environment, to an acceleration of the normal atretic processes or to an inherent incapability of an XX germ cell to perform the successive mitotic divisions necessary for spermatogenesis but not required for oogenesis (Mystkowska and Tarkowski, 1968; Hamerton et al., 1969, 1970).

8. In the male, aneuploid sex chromosome complements such as 47, XXY; 48, XXXY and 49, XXXXY lead to sterility and an abnormal male phenotype. This is accounted for on the present hypothesis by the Y chromosome activating the medullary stimulating gene on the euchromatic X causing testicular development followed by abnormal regulation of steroid and developmental pathways resulting from the presence of an excess X heterochromatin.

Intersexes

The next thing to be discussed is the intersexual states and sex differentiation. According to their cytogenetic expressions, the intersexes can be of two types which are mixoploids and non-mixoploids.

The 46, XX males and the 46, XY females have been considered as the extreme ends of a series of abnormal
sexual phenotypes in between which comes the male pseudohermaphrodites and true hermaphrodites. The XX males and XY females can be considered as the examples of complete sex reversal, whereas the true hermaphrodites are only partially sex reversed and hence intersexual. Hamerton (1971) in his review of human cytogenetics has beautifully summarized the interrelationships between the various categories of intersexes which appear to be most convincing. In the scheme he put forth, he assumed that there is a sex limited autosomal recessive gene with variable penetrance and its expressivity affects sex determination in the male and female foetuses by modifying the action of the controlling centres on the Y chromosome in the male and the X chromosome in the female.

In the male (XY) this locus blocks or partially blocks medullary stimulation. This results either in a complete failure of testicular development as in XY pure gonadal dysgenesis or perhaps in delayed testicular development. This would lead to an incomplete masculinization by the testis or perhaps to the production of foetal masculinizing hormones after the period of maximum target tissue sensitivity had passed. The result of this
would be the development of a male pseudohermaphrodite
or if the cortex develops, of an XY true hermaphrodite.

On the other hand, in the female, a complete
blockage of any stimulation of the indifferent gonad
will result in XX pure gonadal dysgenesis. Partial stimu-
lation of the medulla will result in testes formation,
which depending on timing and amount of secretion of the
masculinizing hormones, will result in the virilized
phenotype of the male pseudohermaphrodite. True herma-
phroditism could result from yet a further variation of
the action of the same locus so that both the medulla and
cortex are partially stimulated. This will result in the
development of an ovotestis or ovary and testis and the
phenotype will almost certainly depend on the timing of
and amount of secretion of foetal testicular hormones. Too
little foetal hormone or its secretion too late will result
in the development of a feminine or virilized feminine
phenotype. Normal secretion will result in the development
of a masculine phenotype. At the extreme end of the scale
in the female we observe complete masculinisation, the
development of testes which secrete normal amounts of
foetal hormones and result in a masculine phenotype with
a 46, XX chromosome complement. This interaction of
testicular development and XX controlling mechanism results
in a phenotype which closely resembles Klinefelter's syndrome. It may be assumed that here the testes are sterile and lack germ cells, not because no germ cells are produced but because XX germ cells are unable to survive in a testicular environment.

Lastly, at the other end of the scale, the male with testicular feminization and a female phenotype probably results from an entirely different gene effect. In this condition the XY genotype mediates testicular development which has a relatively normal hormonal spectrum. However, it would seem that the genetic effect is at the level of the target organs which are completely insensitive to testosterone and that their estrogen sensitivity is not normal, the result is a sterile female phenotype with testes and fairly normal, if infantile, female external genitalia.