CHAPTER VII

CHROMOSOMAL ABERRATIONS IN MALE REPRODUCTIVE PERFORMANCES
The term, "infertility" includes both subfertility and absolute sterility. Biologically it implies that the capacity for producing offspring is diminished statistically it is observed as a reduction in actual numbers of offspring produced, Chandley 1979. 

The subject of human infertility, and the contribution made to it by genic and chromosomal factors, is rather very complex and could only be dealt in a superficial way. Penrose 1963 suggested three major groupings for infertility.

In the first group, he placed those individuals who carried a "lethal condition" and infertility in them simply occurred because they could not survive to reproductive age. These being killed by genes or chromosomal aberrations that they carried, which, in man are viewed as causes of pregnancy wastage exemplified by miscarriages, still births and neonatal and infant deaths. The chromosomally abnormal lethal and sublethal types in this group includes, most autosomal trisomies, triploids and other unbalanced or aneuploid types.
In the second group, he placed those individuals who were rendered infertile by hereditary mental or physical disorders, that obviously excluded them from establishing a normal heterosexual relationship. Individuals with such "hereditary conditions", by him, included majority of cases of Down's syndrome and some other autosomal and sex-chromosomal aneuploidies.

In the third group he included those individuals whose general health was not seriously disturbed, by the abnormalities that they carried but who showed infertility through some genic or chromosomal condition which specifically affected their gonads. Members of this group the "infertile viable types" may marry, but subsequently realization of childlessness may lead them to seek advice at a clinical level.

This chapter is correlated with the typology of the chromosomes and infertility and subfertility of the male under study.

There is sufficient literature available on the karyotyping of the chromosomes related to sex chromosomal aberrations. It can further be added that the anomalies or aberrations related with these chromosomes draws a considerably broad conclusions. Following is the brief review of the literature so far available related to the present study.
Barr and Bertram 1949 observed a distinct chromatin mass, or body, in interphase cells from the brain of the female cats, before the rapid development of the blood-culture technique for studying human chromosome was brought to practice, Chandly 1979. Later in 1955, the buccal smear test was introduced by Moore and Barr, which showed a distinct mass in females only, and this body became to be known as the sex chromatin or Barr body.

In 1959, Jacobs and Strong in Edinburgh discovered the presence of chromatin-positive with the features of Klinefelter's syndrome, its chromosome number being 47 and its constitution being XXY. In individuals with this particular condition, the testes are devoid of germ cells, except in the rare cases where mosaicism is suspected, and the individuals are azoospermic.

In about 1 in every 1,000 male births, there appears a boy who seems quite normal until the onset of puberty. Partial breast development may be seen at puberty, a less female characteristics, a slight altered set of bodily proportions with some what narrow shoulders and a bit larger hips than are typical of normal males. Such person with the Klinefelter's syndrome may be taller than average. Generally there is a deficiency of the male hormone level, which usually results in sparse and female distribution of pubic hair, small testicles,
and some what high-pitched voice. Such type of person may appear to be perfectly normal male and may marry, but usually is completely infertile. It is believed that about 5 per cent of all men who appear at infertility clinics prove to have this syndrome.

The testis being smaller than normal on testicular biopsy shows a remarkable change in the seminiferous dysgenesis. The pathogenesis of Klinefelter's syndrome is obviously obscure. The basic feature of sex chromosome fault lies with the sex determining genes in the zygote, a crossing over between an X-sex chromosome bearing female determining genes and a Y-sex chromosome bearing male determining genes, that prevents the normal development or functioning of testicular tissue, Novak et al. 1971.

"Non disjunction" at one of the two mitotic divisions during spermatogenesis results in a gamete with 24 chromosomes instead of 23 chromosomes. This becomes the probable reason for the origin of trisomy, which actually means the occurrence of 3 chromosomes of one type. Klinefelter's syndrome a total infertility in the male, is the result of the origin of the trisomy, in the sex chromosomes, that is, XXY. As mentioned earlier it occurs 1 in every 1000 males, the most commonest syndrome of all sex anomalies.
Hence sexual disorders in the male may be present in many forms. Some could be due to faults arising in the mechanism of sex determination as early as conception, others due to errors later in sexual differentiation of the embryo and foetus, and after birth, in sexual development. Abnormalities of the sex chromosomes may be associated with the failure of sexual development so that the individual may show some of the characteristics of both the sexes. The term hermaphroditism is reserved for patients in whom male and female gonadal tissue is found to exist, it occurs much less commonly than the intersexes, Menon et al. 1983.

Additional X chromosomes may be recognised by examination of a buccal smear for Barr body, but usually confirmation requires a full karyotype analysis. Seminal analysis is a simple procedure and a low sperm count, or the presence of abnormal and immobile forms may be detected in this way. Testicular biopsy as mentioned earlier frequently provides valuable information on the development of the spermatic tubules and also on the maturation of the germinal epithelium.

The XYY syndrome on the other hand has become widely known since Jacobs et al. 1965 carried out a survey of patients who were mentally subnormal and under
surveillance in a special institution because of "dangerous, violent, or criminal propensities".

The mean stature of these patients is appreciably taller than in the population from which they come. Many of these individuals show a normal sexual development and are fertile, hypogonadism however, has been described. The incidence of XYY karyotype male newborns showed a frequency of around 1:1, 100 similar to that of Klinefelter's syndrome, Vogel Motulsky 1982.

Equational division nondisjunction is clearly involved in producing males with two Ys. During sperm maturation the haploid cell bearing a single Y chromosome with two chromatids fails to separate and distribute the chromatids to the two formed by the equational division. Thus an egg fertilized by that sperm results in a new (2N + 1) cell that is XYY, Carlson, 1984.

Males with XYY have a highly variable response to the extra Y. Most are tall and heavily acned in adolescence. A few are even sterile. Some are mentally retarded and many have behavioral disorders. Over past 3 decades it was believed that the XYY condition results in violent or aggressive behaviour. This is always not true, because some attempts to detect aggressive behaviour in these male individuals with XYY chromosome constitutions are severe oligospermic, Ghosh et al. 1986.
It is believed when an androgens are administered to a female frog, Wachtel, 1975b, genetically female by nuclear sexing, at a critical stage of development, testis will be seen to develop instead of ovaries. Thus hormonal unbalance can also be a factor of an inborn error for a female-to-male, sex reversal. The anatomical characteristics of the male are influenced by essential hormonal factors, particularly endrogen secretion.

There are some other chromosomes which remain responsible for infertility in male individuals.

Polymorphism of the Y chromosome had been observed early in cytogenetics studies. Bender and Gooch 1961 were first one to indicate of the existence of a long Y chromosome in general normal population, while the detection of short Y chromosome was given by Muldal and Ockey, 1961; Bishop et al., 1962; de la Chapelle et al., 1963; Court-Brown et al., 1966; Makino et al., 1963, confirmed the variation in length of the Y chromosome. Cohen et al., 1966 also observed size differences in ethnic groups. The length of Y chromosome being heritable from father to son, and its variabilities existing from family to family, and the variability attributable to the long arm variation was reported by Mckenzie et al., 1972. These variations in the length has been associated with the variations of terminal fluorescent region, Borgaonkar and Hollander; 1971;
Knuutila and Gripenberg, 1972; Laberge and Gagne, 1971; Lewin and Conen, 1971; Robinson and Buckton, 1971; Tishler et al., 1972; Wahlström, 1971. Schnedl, 1971a and Bobrow et al., 1971 have quantitatively shown variation of the length of the fluorescent segment. Schnedl 1971a has reported of the proximal part of the long arm of Y chromosome also shows variability in size.

The length variations of Y chromosome in couples with spontaneous abortions

Increased rate of abortion have been observed in families who are carrier of long Y chromosome, as early as in 1969 by Kadotani et al. and also by Patil and Lubs in 1977. In 1982 Adzic et al. gave an evidence of Yq- and Yq+ variants associated with difficulty in reproduction. In a study conducted by Westake et al. 1983, no significant difference was observed amongst males with long Y chromosomes whose wives had a history of repeated spontaneous abortions and males with mental retardation. They concluded that wives of long Y chromosome males were more likely to have at least one abnormal male birth as compared to those wives whose males Y chromosome length was not significantly increased bore male offspring with various abnormality. Higher frequency of long Y chromosome was the significant characteristic of affected males, whose wives were proven to have undergone 2 or more spontaneous abortions with some other pregnancy abnormality outcome.
Vedebéch et al. in 1984 investigated children in Denmark and reported 2.6% long Y chromosome variants had significantly increased postaglandin stimulation labour in the mothers of the Y chromosome long boys. Such boys suffered more frequently from intrauterine asphyxia leading to an acute caesarean section. Thus they concluded that long Y chromosome fetuses were to be regarded as being a carrier of complications at the time of birth.

First trimester spontaneous abortion and its relationship with the long Y chromosome has been reported by Verp et al., 1983. Variation in Y long chromosomes among the cells of different individuals was standardized by the use of the ratio of the length of the Y chromosome to the average of the lengths of the No. 20 in the same cell. These groups were studied:

(i) men whose wives had 3 or more spontaneous abortions and no-live born infants;

(ii) men whose wives had both, abortions and normal live-born infants; and

(iii) control men whose wives had normal live born infant only.

The human Y chromosome has since long been a favourite target for molecular analysis because primarily of its crucial role in male determination and spermato-
genesis and secondarily because of its postulated evolutionary existence homologously with its counterpart the X chromosome.

Resume of existing literature on chromosome heteromorphisms: The length variants of Y chromosome in patients with reproductive failure.

The length of the Y chromosome varies from individual to individual. The longer Y chromosome, is known to be as long as the chromosomes belonging to the D group, while the shortest to the best of knowledge is less than half length of the chromosome belonging to the G group.

Alvesalo and de la Chapelle, 1981 have claimed that azoospermia, in some, but not all males show deletions of Yq on the locus causing infertility, on the other hand Tiepolo and Zuffardi, 1976, proved that males whose Y chromosome had Yp deficient remained nonfluorescent. Male infertility and even azoospermia are relatively common; thus, sex chromosomal abnormalities might be coincidentally associated.

The variability in the length of the Y chromosome is normally due to the difference in the length of heterochromatin and euchromatin as has been stated by Tiepolo and Zuffardi 1976; Verma et al. 1978. Mchenzie et al. 1972 however states that extreme length variability of
Y chromosome in human is present in normal as well as physically abnormal individuals. Verma et al., 1978 however has suggested that the biological and clinical significance of the Y chromosomes heteromorphism is poorly understood.

This variation in length of Y chromosome on the contrary is a well established fact as numerous cases have been described in which abnormally long Y chromosome is present, Makino and Takagi in 1965. It has been observed that the usually long Y chromosome could be present in both healthy individuals as well as patients with congenital disorders such as Down’s syndrome, Marfan’s syndrome, mental retardation, heart defects, hypogonadism, or male pseudohermaphrodites.

As mentioned earlier the cause of abnormal length of the Y chromosome is still not very clear, but it has been suggested in Nuzzo et al. 1966 article, that the variability in the length of Y chromosome could be due to minor degree of spirilisation of the chromosome or it could be due to an increased amount of the chromosomal material as a result of translocation or duplication. Bishop et al., 1962; Gropp et al., 1963; de la Chapelle and Hortling, 1963; Makino et al. 1963; Tonomura and Ohno, 1963; Kato et al. 1965; and finally Makino and Takagi in 1965 have suggested that whatever the nature of the structural change in the Y long chromosome,
abnormality seems always to be a heritable characteristic.

Wennetrom and de la Chapelle 1965, and Kikuchi and Sandberg 1965 had performed a study of quantitative uptake of tritium labelled thymidine in the cells obtained from the males with long Y chromosomes and those with Y chromosome of normal length. They observed and stated that difference in the size of the Y chromosome was a morphological feature without depicting any functional significance as they observed no difference in the amount labelled on the Y-chromosomes. Later Court Brown 1967 assumed reasonably that the distal half of the long arm of Y chromosome being largely composed of heterochromatin and hence was genetically determined.

Resume of existing literature on male infertility and subfertility: Variabilities in the patients due to sex chromosomes

Chromosome analysis was performed on a 13 years old man by Ataya, Khalid, M., Gertrud-Dubin and Adnan Mrouch 1983 who showed a dicentric 46, X, i(Yq) chromosomal abnormality, an azoospermic and 1st phenotypically male with this karyotype was ever reported.

Unique Y/Y translocation was observed in an azoospermic male by Butler et al. 1982. The Y/Y translocation was a monocentric and submetacentric and had no mosaicism in the infertile male who was tall statured. The azoospermia and infertility in the patient, in
contrast to his father, suggested that infertility was specific of Y/Y translocation.

In a 30 years old azoospermic male, chromosome analysis revealed an apparently balanced Y-autosome reciprocal translocation, t(Y; 6)(Yp 6p; Yq 6p) by Viguie et al. 1982. Testicular biopsy done by them showed an arrest of spermatogenesis at 1st metaphase stage of meiosis.

Another balanced reciprocal translocation in a phenotypically normal man, between the chromosome 2 and 13 was observed by Moraitou et al. 1983. His karyotype was 46XY, t(2;13)(q37;q15) the man was said to suffer from azoospermia, and showed an arrest in spermatogenesis at the spermatocyte stage.

Laurent et al. 1982 observed a reciprocal translocation between chromosomes Y and 17 in an azoospermic infertile male. Cytogenetics studies in a Y to X translocation was observed by Kiyomi et al. 1982. Three members of 1 family with evidence of infertility in male carrier and, where the mother and the 2 sons aged 30 years were reported to be the carrier of Y to X translocation: der(X)t(XY) (p22; q11), all the three carriers have short stature and disproportion of extremities, but otherwise phenotypically normal. The sons were found to be sterile and azoospermic.

Hidek et al. 1982 observed male syndrome in a 29 years old individual, 154 cm in height, 63 kg in weight,
gynecomastia was unnoticed and identification of azoospermia was observed. New evidences from X/Y translocation in a 33 years old azoospermic male was observed by Zuffardi et al., 1982. The patient had a 46X, t(X/Y) (Xq ter → p 22.3 :: Yp 11 → Yp ter) translocation and was H-Y antigen positive. The gene controlling H-Y antigen from the terminal portion of the short arm of the Y chromosome was excluded, yet, another role of Yp in sex determination has been described by the authors.

Resume of existing literature on male infertility and subfertility: Variabilities in the patients due to autosomes

As it has been already mentioned that balanced Robertsonian translocation seems to be some times the cause of infertility in male carriers. The frequency is also increased in reciprocal translocations in male patients of subfertility, oligospermia in such patients seems to be the resultant.

Robertsonian translocations have been reported between the chromosomes 13/14, 21/14 and 22/14, carriers of these translocations, are azoospermic and oligospermic which has been reported by Fracarro et al. 1977.

Chandley et al. 1982 proved that a balanced 21q, 22q Robertsonian translocation ascertained infertility in a phenotypically normal male, chromosomal analysis performed on the patient's parents, by them, showed, that translocation arose from a new mutation in
the subject. The subject was said to suffer from oligo-
spermia and had high frequency of morphological abnormali-
ties, his testicular histology was normal but his meiotic 
investigations showed a chain 0 trivalent in all primary 
spermatocytes.

Males with a DqDq translocation, usually between 
the chromosomes 13 and 14, have repeatedly, been found 
to suffer from decreased fertility, often caused by oligo-
spermia. Though this is by no means a general feature 
in such carriers. Nielsen and Rasmussen 1976, have 
reported 8 DqDq translocation carriers amongst 233 males 
with oligospermia, which amounted to 3.4 per cent as 
compared with 0.1 per cent in newborns. The actual 
reason for the occasional infertility due to DqDq trans-
location carrier remains to be untold story.

As it has been already mentioned that balanced 
Robertsonian translocation seems to be some times the 
cause of infertility in male carriers. The frequency 
is also increased in reciprocal translocations in male 
patients suffering from subfertility. Oligospermia 
in such male patients seems to be the result of arrested 
spermatogenesis as has been already reported by Chandley 
et al. 1975. Searle et al. 1978 reported an incidence 
where the male mice was a translocation carrier ranged 
from fertility to a totally ceased spermatogenesis at 
the onset of meiosis.
There are several authors other than the ones mentioned here, who have laboriously worked on varied translocations with relation to infertility and subfertility in males, but there has been certain findings of infertility in male with regards to chromosomal inversions.

Andras et al. 1982 observed a pericentric inversion of chromosome number 1, which eventually lead to give rise to infertility or azoospermia in the patient. The patient otherwise was observed to have a normal Y chromosome, the patient's mother too was reported to have the similar inversion as her son.

Yet another pericentric inversion of chromosome 1 in a 3 sterile brothers, who being phenotypically normal, was reported by Alejandr et al. 1981. One of the three brother was observed to suffer from azoospermia while the others were reported to be oligospermic.

Infertility or subfertility in a male may be a cause of sperm defect, whether in spermatogenesis or in the germinal epithelium, before the onset of spermatogenesis. When this defected sperm fertilizes an ova, either the zygote is expelled out, or otherwise would give rise to a malformed fetus.

Exclusive selection of the couples for karyotype, numbering 112 of which 8 females other than the total number were, G and C banded, for the actual variability.
PLATE 4. KLINEFELTER'S SYNDROME, WITH CHROMOSOMAL CONSTITUTION AS XXX, CAUSING INFERTILITY IN A MALE PATIENT (CONVENTIONALLY STAINED). [950 magnification]

PLATE 5. A MALE PATIENT WITH XXX SYNDROME, SUFFERING FROM SUBFERTILITY (CONVENTIONALLY STAINED). [950 magnification]
if, at all it existed, Blood sample of male individuals were brought for laboratory detection.

Semen analysis of the individuals showing variability in the sperm count, by pathologist, revealed infertility or subfertility or in other words azoospermic or oligospermic respectively in the sample which were brought for karyotyping. As mentioned earlier individuals suffering from tuberculosis and nutritional deficiencies were karyotyped but not, on the basis of their being azoospermic or oligospermic as occurrence of this variability could exist due to the infections mentioned.

Out of 112 male individuals from the samples undertaken to study only 2 individuals were observed to carry chromosomal aberration with XXY and XYX sex chromosome constitution, an obvious cause of infertility and subfertility in the individuals (Table 7.1).

The occurrence of sex chromosomal aberration was noticed in the individual after 4 years of duration of marriage, the percentage frequency for this trait was 0.89, which was more or less similar to the individual after 5 years of duration of marriage. In conclusion the result obtained from the observed data it could be assumed that sex chromosomal anomaly is a rare phenomenon which usually leads an individual to remain infertile (Table 7.1).
Table 7.2 determines the condition of infertility and subfertility on the basis of reports obtained on semen analysis from the pathologist. It is also further added that the present data has been compared with that of Ghosh et al. 1986. It is evident from the Table 7.2 that in comparison to Gosh et al. 1986 for the incidence of Aspermia, no incidence was observed in the present study. However, percentage frequency for azoospermia amongst 112 infertile males was comparatively very low with that of Gosh et al. 1986, the percentage frequency being only 0.89 of the present study, thereby showing a significant difference in the percentage frequency with this type of affliction.

Subfertility due to oligospermia displayed a very less percentage frequency as compared to the study done by Ghosh et al. 1986. Again a significant difference is noticed in the percentage frequency and also in chromosome constitution.

Marked difference in percentage frequency was observed for occurrence of asthenospermia, as compared to Gosh et al. 1986, negligible percentage frequency was observed in the present study.

From this study of comparison it could be concluded that the prevalence of various types of factors leading an individual to remain infertile and subfertile is observed very rare in the present study as compared to Ghosh et al. 1986.
From this study it can thus be concluded that the prevalence of various types of infertility is very rare as compared to Ghosh et al. 1986.

A further proof of the fore said statement is lent by the process of karyotyped individual whose semen analysis revealed their being infertile or subfertile.

It is noticed from the table 7.3, that out of 112 individuals a single solitary case responded to percentage frequency 0.89 for infertility or azoospermic in the individual married for over 4 years of duration.

More or less similar trend was noticed in the individual suffering from oligospermia or subfertility, Incidence of this variability was observed in the individual married for over 5 years. Hence it could be thus concluded that infertility in a couple due to this chromosomal constitution was observed in a rare frequency in the infertile or subfertile males in the present study.

Table 7.4 reveals the various types of chromosomal constitution in relation to infertility and subfertility in male individuals.

It is evident from the same table that percentage frequency for sex chromosomal constitution 47, XXY represented 0.89 percentage while that of 47, XYY also represents the same percentage frequency.
The other categories of chromosomal constitution did not represent any percentage frequency. Nevertheless infertility or subfertility could also be determined with mentioned chromosomal constitution.

Hence it could finally be concluded that only 2 infertile males out of 112 males represented the sex chromosomal constitution. The other 110 male individuals karyotyped showed normal chromosomal constitution.

Phenotypically the patient with sex chromosomal constitution XXY, a Klinefelter's syndrome had slight mental retardation. The patient had a normal libido and potency was also satisfactorily performed at coitus which was not considered abnormal clinically. His buccal smear showed positive chromatin, hence his karyotype was 47, XXY clinically his testis were small but relatively his external genitalia were quite normal, married for over 4 years, the couple remained infertile.

The second patient was a subfertile male with severe oligospermic, showed no mental retardation, his karyotype exhibited a sex chromosome aberration with constitution XXY. Phenotypically he was normal the height being around 6 ft. Married for over 5 year the couple remained childless.