and A. Svejgaard. Munksgaard Copenhagen/Willaims-Wilkins 1977.
57 Van Enden, W., De Vries, R. R. P., and Van Rood, J. J., The genetic approach to infections disease with special emphasis on the MHC. Dis. Markers *1* (1983) 221-242.
58 Vogel, F., and Motulsky, A. G., Human Genetics. Springer-Verlag, Berlin 1982.
59 Wainscoat, J. S., Bell, J. I., Thein, S. L., Higgs, D. R., Sarjean, G. R., Peto, T. E. A., and Weatherall, D. J., Multiple origins of the sickle mutation: evidence from β^S-globin gene cluster polymorphisms. Molec. Biol. Med. *1* (1983) 191–197.
60 Woolf, B., On estimating the relation between blood group and disease. Ann. hum. Genet. *19* (1955) 251–253.

0014-4754/86/101102-08$1.50 + 0.20/0
© Birkhäuser Verlag Basel, 1986

The genetics of human reproduction

by A. C. Chandley

MRC Clinical and Population Cytogenetics Unit, Western General Hospital, Edinburgh EH4 2XU (Scotland)

Key words. Gonadal failure; impaired gametogenesis; human reproduction; meiosis; aneuploidy; maternal age effect.

Introduction

The attainment of full fertility in any organism requires the proper development and functioning of the reproductive system and survival of the foetus to term. Factors which operate to interfere with any of these processes will disturb the normal pattern and lead to partial or complete infertility.

The reproductive disorders of man are many and varied, but it is the contribution made by genetic anomalies which will be considered in this review. Mutations are known which affect gonadal development and sexual differentiation as well as those which act to disturb gametogenesis. Chromosomal abnormalities too can disturb gametogenesis; they also contribute significantly to human foetal wastage.

Several previous reviews on various aspects of the subject have been written and to these, the reader is also referred[24, 28, 31, 47, 54, 77, 123, 143]. A review of the genetic causes of sterility in the mouse, a much more widely investigated species, has been given by Searle[122].

1. Gonadal failure and impaired gametogenesis

1.1 The effect of the sex chromosomes

Considering that the X and Y chromosomes play a key role in sex determination and differentiation, it is hardly surprising that mutations at the gene loci involved, or sex chromosome imbalance, will produce serious consequences for the development of the reproductive system. Hermaphroditism, sex reversal and infertility are all well-documented features[54, 123].

In human cytogenetics, the discovery that sex chromosome aneuploids like 45, X and 47, XXY, could be associated with infertile syndromes, led to the initiation of chromosome surveys among selected groups of individuals experiencing reproductive problems. In one of the earliest studies, Jacobs et al.[79] examined the karyotypes of 32 women who had never menstruated spontaneously. Sex chromosome abnormalities were found in half of them: These included six with an XO genotype, five with sex chromosome mosaicism, three with a morphologically abnormal X chromosome, and two with an XY sex chromosome complement. This high level of sex chromosome abnormality compared with a frequency of only 1.8 per 1000 among newborn females[78]. The association of a male (XY) genotype with a female phenotype characterizes the two conditions of sex reversal, 'testicular feminization' and 'pure gonadal dysgenesis'[47]. The defect in XY females heterozygous for the X-linked Tfm (testicular feminization) gene[97] is well known, this mutation acting at the most fundamental level to disturb sex differentiation. In pure gonadal dysgenesis, gonadal failure is the primary defect and streak gonads are usually found[47]. In the XO female with Turner's syndrome and the XXY male with Klinefelter's syndrome, gonadal failure appears to relate to germ cell atresia. Recent insights into the role of the sex chromosomes in gamete survival in the mouse have been gained[93]. It would appear that shortly after birth in that species, a second X chromosome blocks male and facilitates female germ cell development. Oocytes at this time are known, both in man[52] and the mouse[42], to have two active X chromosomes, and germ cell loss in XO females may therefore relate to deficiency of X gene products[12, 89]. In XO human females, germ cell loss occurs principally around the time of birth[23, 124], the adult ovary being represented generally by a streak gonad. Nevertheless, limited fertility is achieved by some Turner individuals who retain oocytes over a much reduced reproductive span[83]. Germ cell loss in XY females with pure gonadal dysgenesis may also relate to deficiency of X-linked products.

The presence of two X chromosomes in germ cells of the mouse appears to be compatible with initiation of development in the male direction but is not compatible with spermatogenesis[93]. The XX component in XX/XY chimaeras appears to degenerate just before birth[94], while in XX, Sxr (sex reversed) males, degeneration sets in soon after birth[25]. On the other hand, spermatogenesis does take place in XO, Sxr males, some germ cells surviving to form spermatids and even a few abnormal spermatozoa[25]. In keeping with these findings, spermatogonia in much reduced numbers have been recorded in the testes of pre-pubertal XXY boys[98], but by puberty, little sign of spermatogenic activity remains. Gonadal failure resembling that seen in adult XXY men is also seen in XX

men[38]. In XX males, the story is complex and the aetiology mixed[38] but current research is showing that at least in some cases, the paternally-derived X chromosome may harbour a testis-determining fragment of Y chromosome transferred to the X by accidental crossing-over or X-Y interchange[15,39,46]. The identification of Y-specific sequences in the DNA of a number of XX males investigated using Y-specific probes[57] supports this.

Whether the Y chromosome functions in spermatogenesis is not clear. In the mouse, it has been argued[93] that the Y chromosome may only serve a role in ensuring normal spermatogenic development to a late stage by providing a pairing partner for the X. (It will be shown later that normal XY pairing must be maintained for meiosis to go to completion). In man, factors which influence spermatogenesis may be situated on the long arm of the Y chromosome close to the intensely fluorescing heterochromatin[11,138].

1.2 X- and Y- autosome translocation

From studies on human female X-autosome translocations, there is evidence that the structural integrity of a critical region of the X chromosome long arm is necessary for normal ovarian function in heterozygotes. Sarto et al.[119] first drew attention to this by pointing out that all females hitherto reported who were heterozygous for a reciprocal X-autosome translocation with a breakpoint in this region had primary or secondary amenorrhoea. Summitt et al.[135] reviewed the literature and found that 9 of 18 females reported to be carriers of X long arm autosome translocations exhibited either streak ovaries (7 cases), ovarian hypoplasia (1 case) or underdeveloped ovaries (1 case). The X chromosome breakpoints of the 13 translocations were all located within the region Xq13-Xq26. The critical region therefore lies in the middle of the long arm and represent about two-thirds of its length. A few exceptions to this general rule have, however, been presented[5,19,95]. These authors have described women heterozygous for a balanced X-autosome translocation with a breakpoint in the critical region but who, nevertheless, were fertile. The question as to precisely how such a chromosome exchange could affect the development and functioning of the ovary remains still to be answered. A 'position effect' explanation has been offered by Summitt et al.[135] while Madan et al.[95] have suggested a mechanism of variable penetrance similar to that which allows some XO women (and XO mice) to retain oocytes into adult life and thus to conceive. Burgoyne and Baker[16] believe that meiotic pairing failure in female X-autosome translocation heterozygotes and also in XO females, could account for the oocyte atresia by selectively removing oocytes from the germ line. Reproductive lifespan is known to be curtailed in some female X-autosome translocation stocks of the mouse, as well as in XO mice, owing to a smaller pool sizes of oocytes[16]. Observations by Speed on foetal XO oocytes in mice[131b] show a tendency on the part of the single X chromosome for self pairing or nonhomologous pairing with an autosome at pachytene in up to 50% of cells. These, Speed suggests, could be oocytes which will survive, having saturated their pairing requirement. Observations made on three XO *human* foetuses, however, showed most oocytes blocked at the preleptotene stage (Speed, in press), germ cell failure at least in these cases occurring before pairing had even begun.

For male carriers of an X-autosome reciprocal translocation, the consequences for spermatogenesis are severe. Meiotic development is invariably arrested at the pachytene stage, both in man[28,45] and the mouse[122], and carriers are rendered severely oligospermic or azoospermic. For male carriers of reciprocal Y-autosome translocations the consequences are similar if perhaps slightly less severe. Spermatogenesis in a few of these cases seems to be able to proceed to the late stages both in man[45,85,127], and the mouse[18,86,122], and in one human case of Y; 10 reciprocal rearrangement[85a] spermatozoa were produced in numbers which were within normal limits for the human male, pregnancy being achieved on four separate occasions. Ascertainment in this case was by birth of a child with congenital malformations.

A hypothesis to explain the sterility of male X-autosome translocation heterozygotes of *Drosophila,* the mouse, and man, has been put forward by Lifschytz and Lindsley[87]. They argue that asynchronous control of X-chromosomal and autosomal gene activity is necessary for normal spermatogenesis. The spermatogenic disturbance in X-autosome carriers, they suggest, is brought about by autosomal interference with the precocious inactivation of X-linked genes. The sterility of Y-autosome translocation heterozygotes might be explicable on the same model since the Y chromosome too is known to be inactivated early in the primary spermatocyte stage both in the mouse[82] and in man[140]. The effects on spermatogenesis in such cases, appear, as far as one can tell from the limited number of reports so far, to be less severe than when rearrangement takes place between an autosome and the X.

1.3 Autosome-autosome translocation

Lyon and Meredith[90] were the first to show that certain purely autosomal translocations of the mouse cause sterility in male heterozygotes because of spermatogenic impairment. The occurrence of such translocations in man has also been noted[29,31]. A mechanism by which purely autosomal rearrangements might bring about spermatogenic disturbance has been put forward by Forejt[49]. He and his co-workers showed that in a number of male-sterile autosomal translocations of the mouse, a high frequency of centromeric contacts between the translocation configuration and the XY bivalent were formed at pachytene[50,51] and particularly when chain configurations were present in the translocation. Such contacts were not seen to any great extent among the pachytene cells of male-fertile translocation carriers showing a preponderance of ring quadrivalents. Similar contacts were reported by Chandley[30] in sterile male mice doubly heterozygous for two partially overlapping inversions. Forejt[49] suggested that non-random associations might produce interference with the precocious X-chromosome inactivation in the primary spermatocyte which, on the Lifschytz/Lindsley hypothesis[87], would be required for normal spermatogenesis. Whether oocyte numbers are lower than normal in human females who carry autosome translocations which sterilize the male is not known but, in the mouse, evidence of reduced ovarian volume indicating an effect of the translocation on oogenesis has

been presented by Mittwoch et al.[103] for the t(11;19)42H male-sterilizing translocation. Burgoyne and Baker[16] have argued that meiotic pairing failure in autosomal heterozygotes of both sexes could again be responsible for the gametogenic disturbances observed.

For human male carriers of a Robertsonian (Rb) translocation, the effects on spermatogenesis are somewhat variable. In the majority of cases, fertility is not disturbed; nevertheless, some Rb heterozygotes are ascertained through attendance at infertility clinics[28, 139]. From family studies of such men, it has been shown that the infertile subjects often have male relatives carrying the same translocation who are themselves fertile, indicating that the translocation itself is not the only and consistent cause of infertility. Genetic background could also be important. Tiepolo et al.[139] have tested the hypothesis that infertility in balanced carriers of human Rb translocations could result from a loss of ribosomal cistrons. However, ^{3}H-rRNA/DNA hybridization experiments in nine infertile translocated patients and their normal and/or translocated fertile male relatives, failed to demonstrate any significant difference in the number of rDNA genes[56].

The majority of Rb heterozygotes ascertained through infertility have been t(13q14q) individuals, this being the most common type of Robertsonian rearrangement in man, although carriers of t(13q15q), t(14q21q), t(14q22q) and t(21q22q) have also been reported[33]. High frequencies of XY-trivalent contacts at pachytene have been reported for the sterile carrier of a 13q14q Rb translocation[88a] and for two sterile carriers of 14q21q translocations[117a]. Contacts occurred principally when unpaired segments were present in the acrocentric short arms of the trivalents.

1.4 Other structural rearrangements

Translocations are not the only structural rearrangements to be associated with germ cell maturation impairment in human males. In an early investigation, McIlree et al.[91] reported on a male showing a small ring-G chromosome (later identified as a ring 21), in his somatic karyotype. At meiosis, spermatocytes at metaphase I showed degenerative changes suggestive of spermatogenic failure and one pair of small autosomes was present always as a pair of univalents: the man was azoospermic. Complete breakdown of spermatogenesis was seen also in a ring-E individual reported by Kjessler[84].

In another report by McIlree et al.[92] spermatogenic failure was noted in a man carrying a dicentric Y chromosome. The X and Y short arms could not pair at meiosis in this man because the short arm pairing region of the Y chromosome was present in the centre of the abnormal chromosome and therefore not available to make end-to-end association with the X. Pairing failure between the X and Y was also noted at metaphase I in a ring-Y azoospermic individual studied by Chandley and Edmond[32]. For both the dicentric Y and the ring Y patient, the suggestion was made that the failure to pair in the XY bivalent was the cause of the breakdown in spermatogenesis. More will be said, however, about meiotic pairing failure and spermatogenic arrest under section vi.

A pericentric inversion in the Y chromosome of another male studied by McIlree et al.[92] did allow for normal pairing and in this case, normal testicular histology was reported. Pericentric inversions in the autosomes have occasionally also been reported among infertile human males. Tiepolo et al.[139] found a pericentric inversion in chromosome 6 in one male from the Pavia sample and Faed et al.[45] reported an inversion 3 in their Dundee study. Other human autosomal inversion heterozygotes have, however, been found to have normal spermatogenesis[142], and certainly, on the basis of the few cases studied to date, a positive association with spermatogenic impairment cannot be claimed for inversions in general. More cases require to be studied.

1.5 Aneuploids

The severe germ-free failure in XXY and XO individuals has been described earlier in the chapter. A number of other human aneuploid situations have also been investigated for their effects on germ cell development. The spermatogenic picture in 47,XYY men, even among those who have been karyotyped for reasons other than infertility, ranges from one of severe impairment to apparent normality[126]. Few XYY spermatocytes have been recorded at metaphase I of meiosis, the surviving germ cells usually showing a normal XY complement[44, 136]. Claims have, however, been made for retention of the second Y in some males, at least until the pachytene[7] stage, and in an XYY male studied by Hulten and Pearson[75], 45% of spermatocytes at diakinesis/metaphase I were found to be XYY. A hypothesis to explain the variable pattern of spermatocyte loss seen in XYY men and mice, based on a disruption of XY pairing, has been put forward by Burgoyne[13] and Burgoyne and Biddle[17].

Trisomy 21 males also show a range of variation in their testicular histology[125] and where meiotic studies have been made, various proportions of metaphase I cells containing trivalents, a bivalent plus a univalent or no obvious extra No. 21 have been recorded[73]. In one pachytene analysis[76] only trivalents were observed. In another[80], no evidence for the extra 21 could be found at this prophase stage of meiosis. The latter authors did, however, see a small extra univalent, interpreted as a No. 21, at metaphase I. Few other autosomal aneuploid situations are viable in man and so little other information can be gained about germ cell survival. One case of mosaic trisomy 8, studied by Chandley et al.[35] did, however, show gross disturbances of spermatogenesis. Although the extra No. 8 was not present at metaphase I of meiosis, a high percentage of spermatocytes containing unpaired sex chromosomes was found at this stage. This, it was suggested, could have been the cause of germ cell failure. A prophase analysis was not carried out in this case.

For female autosomal aneuploids, there is evidence of germ cell atresia both in the ovaries of trisomy18[1, 118] and trisomy 21[61, 110] girls.

Studies at meiosis in trisomy 21 foetal oocytes[131, 144] show a mixture of trivalent, bivalent plus univalent and apparently normal diploid configurations at the pachytene stage. Trivalents are observed in about one third of cells, a proportion of these showing triple association along certain segments.

The mechanism responsible for germ cell failure in these female, as well as male, aneuploid situations is not yet fully understood but there does appear to be variable

penetrance and a range of severity in the effects on gametogenic development observed. Meiotic pairing failure has been suggested by Burgoyne and Baker[16] to play a role, and when more cases have been assessed, it may turn out that a relationship exists between the relative proportions of the different meiotic pairing configurations and levels of germ cell atresia recorded.

1.6 Meiotic pairing failure

Several reviews have already been written on the possible association between failure of pairing and failure of gametogenesis[16, 31, 101]. Miklos[101] has suggested that a saturation of pairing sites between homologous chromosomes is essential for regular meiotic and post-meiotic development of germ cells. On this model, not only could XY pairing failures be accommodated but also autosomal failures both in males and females. Sometimes, pairing failure affects only one pair of chromosomes in the complement, on other occasions it may affect many pairs. In man, the germ cell failure of those patients showing extremely low chiasma counts, perhaps due to meiotic mutation, appears to relate to generalized pairing failure[26, 137]. A raised frequency of synaptic anomalies among the autosomal bivalents of oligo- and azoospermic men attending infertility clinics has been reported by Egozcue[41]. Among human foetal oocytes, frequent errors of synapsis in the prophase stages are observed[131a]. Speed[131a], who has made extensive observations at the electron microscope level on human oocytes prepared by spreading, recorded single or multiple pairs of univalents in about 10% of all pachytenes analysed and partial asynapsis in at least one complement in a further 8% of cells. Occasional oocytes contained up to seven such partially asynaptic bivalents. An interesting observation was the thickening of unpaired segments of chromosomes and univalents, with the appearance of excrescences along the axes, comparable in appearance to those exhibited by the differential axes of the X and Y in the male[34]. Speed[131a] observed a lower frequency of synaptic anomalies in later pachytene stages, indicating selective loss of such cells from the germ line. It was suggested that the thickenings and excrescences observed along the unpaired axes could correlate with a state of genetic inactivation brought about by pairing failure. Certainly it seems that much more needs to be found out about pairing and germ cell loss before an understanding of the problem can be reached. In situations where germ cell development is arrested in very early prophase, before pairing commences, an alternative explanation would require to be found.

2. The nature and extent of XY pairing

Although a great deal of meiotic investigation in man has taken place over the years using air-drying techniques (see refs 27 and 74 for reviews), recent developments in spreading methods[104, 105] and serial reconstructions of primary spermatocytes[62–67, 113–115] have provided new insights into events taking place at meiotic prophase. One item of particular interest relates to the question of pairing and homology within the human XY bivalent at early pachytene.

From air-dried observations at metaphase I, when the human X and Y are in end-to-end association, it is known that pairing takes place between the respective short arms (Xp and Yp) of the two chromosomes[36,109]. From serial reconstructions of pachytene spermatocytes, an extensive pairing segment within the sex pair, complete with synaptonemal complex, has been found[130]. Synaptonemal complex presence was formerly taken to imply homology within synapsed regions of chromosomes, but a number of investigations have now shown that this need not necessarily be the case, normal-looking complexes being found even within regions of known genetic dissimilarity[104, 107].

From measurements made on meiotic cells prepared by spreading, the human XY pairing segment at early pachytene (the stage at which a maximum length synaptonemal complex is found) occupies, on average, about 10% of total X axial length and 30% of Y axial length[34, 106, 129]. Centromere positions in the human X and Y are difficult, if not impossible, to pinpoint in spread preparations at pachytene because of the large number of excrescences along each of the sex chromosome axes. Moses et al.[106] have however, concluded that the pairing segment involves the distal one third of Xp and about 90% of the short arm of the Y, and this had become more or less the accepted dogma[14, 37, 111, 120]. Recently, however, a more extensive analysis of human pachytene spermatocytes prepared by spreading[34], has provided circumstantial evidence that in some cells at least (about 5% of all early pachytene spermatocytes analysed), a greater proportion of total Y length (50–70%) can be involved in pairing with Xp. A pairing segment involving more than 50% of total Y length would of course imply that the Y centromeric region and proximal Yq, in addition to all of Yp, be held in synapsis with distal Xp. Indeed the authors suggested that all of the euchromatic portion of the human Y might be capable of synapsing with Xp.

Since pairing of a centromeric region with a non-centromeric region would seem to have to take place by non-homologous association, it is worth considering whether homology exists in other regions, especially distal XpYp, and if so, does crossing-over occur there? Various models predicting the occurrence of an obligatory crossover in the human XY pairing segment have been proposed[11, 14] but genetic evidence for crossing-over and partial sex linkage in man is lacking. Recombination bars or nodules, taken as indicative of crossing-over[21, 22] have, however, been noted in the human XY bivalent[65], and some molecular and genetic evidence exists for homology within the distal tips of Xp and Yp[53, 112]. Moreover, a tiny segment of distal Xp and Yp has been seen to remain synapsed throughout the whole of the pachytene stage even after the X and Y axes have desynapsed over the rest of their lengths[34]. Whether this too reflects homology within this segment can, however, only be speculated upon.

The recent elucidation of sex-reversal (Sxr) in the mouse, has shown that crossing-over is a regular occurrence at the distal tip of the XY pairing segment in XY, Sxr males. Evans et al.[43] who found cytological evidence for a small reciprocal exchange between X and Y in these animals, have suggested that regular exchange might also occur in the XY bivalent of normal male mice. This could be the case also in the human male, evidence for the exchange of hypervariable telomeric sequences on the human Y chro-

mosome, to the X, having recently been found[36a]. There are, on the other hand, those who argue that pairing between the X and Y in male mammals in a special case of non-homologous synapsis[3], association between the sex chromosomes having been retained simply as a mechanism to ensure regular segregation in the sex bivalent. Any exchange events which took place, as for example in Sxr males, would then be regarded as non-homologous interchanges and not true crossover events. The X-Y interchanges which have been suggested to give rise in man to some XX males[15, 39, 46] could also arise, not by true crossing-over, but by non-homologous exchange. The location of the testis-determining gene in the paracentromeric region of the Y chromosome[11] would, of course, make any such exchange event necessarily take place very close to the Y-centromere, a region which normally tends to inhibit crossing-over[6]. The finding of a physical association between the Y centromeric region and Xp in some cells[34] could, however, provide the opportunity for exchange.

3. Biochemical studies on human spermatocytes

Despite large gaps in the knowledge, it now seems clear that the programme of molecular events taking place at male meiotic prophase has been conserved during evolutionary time: in spite of the broad phylogenetic span, species as diverse as lily and the mouse show great similarity in the biochemical processes relating to pairing and crossingover[72, 132, 133]. Studies in human testicular tissue have been carried out to a lesser extent, mainly on account of the technical difficulties involved in effecting good cell separations but some data are nevertheless available[134]. These show that, in common with lily and the mouse, a controlled nicking of DNA and a repair activity localized in moderately repeated regions of the genome, are associated with the late prophase interval and thought to be related to the recombinational phase of meiosis. This DNA activity is complemented by activation of specific groups of proteins (the U- (unwinding) and R- (reannealing)proteins) which affect the secondary structure of DNA and show characteristic cyclic behaviour during the prophase of meiosis[70, 71].

Successful studies have also been made of RNA metabolism during meiotic prophase in the human male[140].

4. Aneuploidy, foetal wastage, and the maternal age effect

Before ending this review, it would seem fitting to record the contribution made by chromosome abnormality and in particular aneuploidy, to the overall levels of foetal wastage in man.

It is now known that about 15% of all human pregnancies end in a clinically recognizable abortion[145] with about 60% of those occurring in the first trimester being chromosomally abnormal[9, 147]. The principal abnormalities found are 45,X (20%), autosomal trisomy (50%) triploidy (17%) and tetraploidy (6%), aneuploidy alone therefore, making up 70% of the cases. Additional losses due to aneuploidy will also undoubtedly occur at or around the time of implantation for, in the mouse, it is known that the majority of autosomal monosomics and some trisomics die at this time[55]. One recent study into early conceptual loss in man, carried out by Miller et al.[102], has attempted to use to rise in urinary levels of βHCG to recognize very early post-implantation pregnancies before they can be recognized clinically. These gave a figure for total postimplantation loss of at least 43%. Using the same assay, Edmonds et al.[40], concluded that ovulatory cycles exposed to the risk of pregnancy carried a 59.6% chance of conception and a 56.8% risk of embryonic loss. This fecundity of about 25% for man is clearly very low but may to a great extent be attributable to lethal chromosome anomalies.

In the past, estimations of the total level of chromosome abnormality at conception in man have been based on the figures obtained by karyotypic analysis of early spontaneous abortions. Because of the unknown contribution made by pre-implantation and early post-implantation losses, however, the figures have been somewhat speculative. Recently, a start has been made on analysing the chromosome complements of early cleaving human embryos obtained by in vitro fertilization[2], but data so far are limited. Of 11 embryos examined for their ploidy, two showed evidence of autosomal aneuploidy. Chromosome analysis carried out on unfertilized human ova have so far proved somewhat uninformative owing to the poor quality of the preparations generally obtained, but significant progress has been made into the karyotyping of human spermatozoa following fusion with hamster eggs[96].

For 1000 sperm genomes analysed, an overall frequency of chromosome abnormality of 8.5% has been recorded, with 5.2% of complements being aneuploid. Were an equal contribution to come from the ovum, a frequency overall of 17% with about 10% aneuploidy would be expected. It is known, however, from the observations of Jacobs and Hassold[77], Mikkelsen et al.[100] and others who have traced the origins of various autosomal aneuploid conditions in man by means of chromosome polymorphisms, that maternal errors outnumber those arising paternally by about four to one. The level of aneuploidy alone among ova could therefore be as high as 20%, giving an overall level of aneuploidy at conception of around 25%. This would be far higher than that found in any other investigated mammalian species[48].

Compared with other mammals, man also shows a striking maternal age effect for trisomy[128], an effect noted, not just for liveborn subjects with trisomy 13, 18 or 21 (see ref. 8 for review), but for the liveborn sex aneuploids 47,XXX and 47,XXY[68] and for trisomic abortuses[60, 121]. The former study has shown that although as a group, trisomic abortuses are associated with a substantial increase in maternal age, considerable differences exist in the magnitude of the effect for different chromosome pairs. The effect is most pronounced for trisomies involving the smaller chromosomes whether acrocentric or non-acrocentric. Trisomy 16 is an exception, however, in being only weakly age-related. It is also exceptional in being the most frequent in occurrence, making up about one third of all trisomic cases[8, 60]. Some trisomies like trisomy 1 are rarely if ever found among abortuses, but may be selected against at a time before a clinically recognized pregnancy is established[81]. First meiotic maternal errors appear to predominate in all trisomic conditions and at all maternal ages, whether or not the particular trisomic condition is strongly age-related[60, 100].

An extremely interesting finding which has emerged recently from the data, however, is that significant heterogeneity exists among trisomics with regard to the proportion attributable to *paternal* nondisjunction. Data for both spontaneous abortions and liveborns suggest that trisomy 21 is more likely to be paternally derived than any other autosomal trisomy[58]. Consideration of the sex ratio in cases of trisomy 21 of known parental origin suggests that an excess of males is associated with paternal first meiotic division nondisjunction, the distorted sex ratio appearing to stem from a mechanism in which the extra No. 21 segregates perferentially with the Y chromosome. The fact that this mechanism of origin is more prevalent in trisomy 21 may well explain why there is an excess of males associated with this particular abnormality but not with other autosomal trisomies[59, 88].

There are those who believe that the maternal age effect for aneuploidy in man could be accounted for on the basis of relaxed selection against trisomic foetuses in the uteri of older women[4]. Strong arguments against this idea have, however, recently been put forward[20, 69, 146]. Experimental studies in the mouse now indicate, in fact, that the rise in frequency of aneuploid embryos, or at least the abnormal chromosome segregation giving rise to them, is an epiphenomenon of ageing in the adult female. Brook et al.[10] have produced data which point to the influence of biological ageing rather than to chronological age per se. Thus, an earlier cessation of reproductive life, brought on by unilateral ovariectomy in CBA females, resulted in the earlier onset of irregular oestrous cyclicity and an earlier rise in aneuploidy. The clinical implications are that the probability of conceiving a Down foetus will be determined by distance in time from the approaching menopause, perhaps because of a diminishing oocyte store. One group of women displaying early biological ageing and conforming well to this model, are those rare individuals with Turner syndrome (XO) who manage to achieve pregnancy during their limited reproductive span. Menopause occurs early in such women, but for their low chronological age they show a remarkably high level of foetal wastage and a greatly increased risk for producing Down syndrome offspring[83, 117].

Brook et al.[10] have suggested that a continuum of age-related aneuploidy might exist in women, governed not by chronological age but by biological age. The biological age-related cases would then be superimposed on non-age related cases, for example those paternally-derived or those due to translocation. Some young mothers of children with primary trisomy 21 might thus be found to have evidence of earlier biological ageing or to be 'at risk' for irregular oestrous cyclicity. Read[116] has proposed that hormonal imbalance prior to the time of conception could be the critical factor in nondisjunction among older women. He believes, moreover, that young pill-users could also be at risk for hormonal imbalance and that this could be the causal explanation of recent data trends which indicate a shift in the incidence of Down syndrome to younger age groups[99, 108, 141]. Further data are required, however, both epidemiological and experimental, before a link between hormones and nondisjunction can be established with certainty.

1 Alexiou, D., Chrysostomidou, O., Vlachos, I., and Deligeorgis, D., Trisomy 18 with ovarian dysgenesis. Acta paediat. scand. *60* (1971) 93–97.
2 Angell, R.R., Aitken, R.J., van Look, P.F.A., Lumsden, M.A., and Templeton, A.A., Chromosome abnormalities in human embryos after in vitro fertilization. Nature *303* (1983) 336–338.
3 Ashley, T., A re-examination of the case for homology between the X and Y chromosomes of mouse and man. Hum. Genet. *67* (1984) 372–377.
4 Aymé, S., and Lippman-Hand, A., Maternal age effect in aneuploidy: does altered embryonic selection play a role? Am. J. hum. Genet. *34* (1982) 558–565.
5 Barnebei, V.M., Wyandt, H.E., and Kelly, T.E., A possible exception to the 'critical region' hypothesis of X-chromosome inactivation. Am. J. hum. Genet. *31* (1979) 88A (Abstr.).
6 Beadle, G.W., A possible influence of the spindle fibre on crossing-over in Drosophila. Proc. natn. Acad. Sci. USA *18* (1932) 160–165.
7 Berthelsen, J.G., Skakkebeak, N.E., Perbøll, O., and Nielsen, J., Electron microscopical demonstration of the extra Y chromosome in spermatocytes from human XYY males, in: Development and Function of Reproductive Organs. Eds A.G. Byskov and H. Peters. Int. Congress Series No. 559. Elsevier/North Holland, Amsterdam 1981.
8 Bond, D.J., and Chandley, A.C., Aneuploidy. Oxford University Press, Oxford 1983.
9 Boué, J., Boué, A., and Lazar, P., Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. Teratology *12* (1975) 11–26.
10 Brook, J.D., Grosden, R.G., and Chandley, A.C., Maternal ageing and aneuploid embryos – Evidence from the mouse that biological and not chronological age is the important influence. Hum. Genet. *66* (1984) 41–45.
11 Bühler, E.M., A synopsis of the human Y chromosome. Hum. Genet. *55* (1980) 145–175.
12 Burgoyne, P.S., The role of the sex chromosomes in mammalian germ cell differentiation. Annls Biol. anim. Biochim. Biophys. *18* (1978) 317–325.
13 Burgoyne, P.S., Evidence for an association between univalent Y chromosomes and spermatocyte loss in XYY mice and men. Cytogenet. Cell Genet. *23* (1979) 84–89.
14 Burgoyne, P.S., Genetic homology and crossing-over in the X and Y chromosomes of mammals. Hum. Genet. *61* (1982) 85–90.
15 Burgoyne, P.S., The origins of men with two X chromosomes. Nature *307* (1984) 109.
16 Burgoyne, P.S., and Baker, T., Meiotic pairing and gametogenic failure, in: Controlling events in meiosis, Proc. 38th SEB Symposium Reading, UK, pp. 349–362. Eds C.W. Evans and H.G. Dickinson. Company of Biologists, Cambridge 1984.
17 Burgoyne, P.S., and Biddle, F.G., Spermatocyte loss in XYY mice. Cytogenet. Cell Genet. *28* (1980) 143–144.
18 Cacheiro, N.L.A., Russell, L.B., and Swartout, M.S., Translocations, the predominant cause of total sterility in sons of mice treated with mutagens. Genetics *76* (1974) 73–91.
19 Cann, H.M., Sakaguchi, S., Stone, J., Gold, E., and Luzzatti, L., Familial X-autosome translocation (X;21). Am. J. hum. Genet. *27* (1975) 23A (Abstr).
20 Carothers, A.D., Evidence that altered embryonic selection contributes to maternal age effect in aneuploidy: A spurious conclusion attributable to pooling of heterogeneous data? Am. J. hum. Genet. *35* (1983) 1057–1059.
21 Carpenter, A.T.C., Electron microscopy of meiosis in Drosophila melanogaster. II. The recombination nodule – a recombination associated structure at pachytene? Proc. natn. Acad. Sci. USA *72* (1975) 3186–3189.
22 Carpenter, A.T.C., Synaptonemal complex and recombination nodules in wild type *Drosophila melanogaster* females. Genetics *92* (1979) 511–541.
23 Carr, D.H. Haggar, R.A., and Hart, A.G., Germ cells in the ovaries of XO female infants. Am. J. clin. Path. *49* (1968) 521–526.
24 Carter, C.O., Genetics in relation to urology, in: Scientific Foundations of Urology, 2nd edn, pp. 335–343. Eds G.D. Chisholm and D.I. Williams. Heinemman, London 1982.
25 Cattanach, B.M., Pollard, C.E., and Hawkes, S.G., Sex-reversed mice: XX and XO males. Cytogenet. Cell Genet. *10* (1971) 318–337.
26 Chaganti, R.S.K., Jhanwar, S.C., Ehrenbard, L.T., Kourides, I.A., and Williams, J.J., Genetically determined asynapsis, spermatogenic degeneration and infertility in man. Am. J. hum. Genet. (1980) *32* 833–848.

27 Chandley, A.C., Human meiotic studies, in: Modern Trends in Human Genetics, 2nd edn, pp. 31–82. Ed. A.E.H. Emery. Butterworths, London and Boston 1975.
28 Chandley, A.C., The chromosomal basis of human infertility. Br. med. Bull *35* (1979) 181–186.
29 Chandley, A.C., The origin of chromosomal aberrations in man and their potential for survival and reproduction in the adult human population. Annls Génét. *24* (1981) 5–11.
30 Chandley, A.C., A pachytene analysis of two male-fertile paracentric inversions in Chromosome 1 of the mouse and in the male-sterile double heterozygote. Chromosoma *85* (1982) 127–135.
31 Chandley, A.C., Infertility and chromosome abnormality, in: Oxford Reviews of Reproductive Biology, vol. 6, pp. 1–46. Ed J.R. Clarke. Oxford University Press, Oxford 1984.
32 Chandley, A.C., and Edmond, P.E., Meiotic studies on a subfertile patient with a ring Y chromosome. Cytogenetics *10* (1971) 295–304.
33 Chandley, A.C., Hargreave, T.B., and Fletcher, J.M., Translocation 21q22q in an infertile human male. J. med. Genet. *19* (1982) 366–369.
34 Chandley, A.C., Goetz, P., Hargreave, T.B., Joseph, A.M., and Speed, R.M., On the nature and extent of XY pairing at meiotic prophase in man. Cytogenet. Cell Genet. *38* (1984) 241–247.
35 Chandley, A.C., Hargreave, T.B., Fletcher, J.M., Soos, M., Axworthy, D., and Price, W.H., Trisomy 8: Report of a mosaic human male with near-normal phenotype and normal IQ, ascertained through infertility. Hum. Genet. *55* (1980) 31–38.
36 Chen, A., and Falek, A., Cytological evidence for the association of the short arms of the X and Y in the human male. Nature *232* (1971) 555–556.
36a Cooke, H.J., Brown, W.R.A., and Rappold, G.A., Hypervariable telomeric sequences from the human sex chromosomes are pseudoautosomal. Nature *317* (1985) 687–692.
37 Cooke, H.J., Schmidtke, J., and Gosden, J.R., Characterisation of a human Y chromosome repeated sequence and related sequences in higher primates. Chromosoma *87* (1982) 491–502.
38 de la Chapelle, A., The etiology of maleness in XX men. Hum. Genet. *58* (1981) 105–116.
39 de la Chapelle, A., Tippett, P.A., Wetterstrand, G., and Page, D., Genetic evidence of X-Y interchange in a human XX male. Nature *307* (1984) 170–171.
40 Edmonds, D.K., Lindsay, K.S., Miller, J.F., Williamson, E., and Wood, P.J., Early embryonic mortality in women. Fert. Steril. *38* (1982) 447–453.
41 Egozcue, J., Templado, C., Vidal, F., Navarro, J., Morer-Fargas, F., and Marina, S., Meiotic studies in a series of 1100 infertile and sterile males. Hum. Genet. *65* (1983) 185–188.
42 Epstein, C.J., Mammalian oocytes. X chromosome activity. Science *163* (1969) 1078–1079.
43 Evans, E.P., Burtenshaw, M.D., and Cattanach, B.M., Meiotic crossing-over between the X and Y chromosomes of male mice carrying the sex-reversing (Sxr) factor. Nature *300* (1982) 443–445.
44 Evans, E.P., Ford, C.E., Chaganti, R.S.K., Blank, C.E., and Hunter, H., XY spermatocytes in an XYY male. Lancet *i* (1970) 719–720.
45 Faed, M.J.W., Lamont, M.A., and Baxby, K., Cytogenetic and histological studies of testicular biopsies from subfertile men with chromosome anomaly. J. med. Genet. *19* (1982) 49–56.
46 Ferguson-Smith, M.A., X-Y chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. Lancet *ii* (1966) 475–476.
47 Ford, C.E., Cytogenetics and sex determination in man and mammals. J. Biosoc. Sci. Suppl. *2* (1970) 7–30.
48 Ford, C.E., The time in development at which gross genome imbalance is expressed, in: The Early Development of Mammals, pp. 285–304. Eds M. Balls and A.E. Wild. Cambridge University Press, Cambridge 1975.
49 Forejt, J., Nonrandom assication between a specific autosome and the X chromosome in meiosis of the male mouse: possible consequence of homologous centromeres separation. Cytogenet. Cell Genet. *13* (1974) 369–383.
50 Forejt, J., X-Y involvement in male sterility caused by autosome translocations – A hypothesis, in: Genetic control of gamete production and function, pp. 135–151. Eds P.G. Crosignani and B.L. Rubin. Academic Press/Grune and Stratton, 1982.
51 Forejt, J., Gregorová, S., and Goetz, P., XY pair associates with the synaptonemal complex of autosomal male-sterile translocations in pachytene spermatocytes of the mouse *(Mus musculus)*. Chromosoma *82* (1981) 41–53.
52 Gartler, S.M., Liskay, R.M., and Gant, N., Two functional X chromosomes in human fetal oocytes. Expl Cell Res. *82* (1973) 464–466.
53 Goodfellow, P., Banting, G., Sheer, D., Ropers, H.H., Caine, A., Ferguson-Smitz, M.A., Povey, S., and Voss, R., Genetic evidence that a Y-linked gene in man is homologous to a gene on the X chromosome. Nature *302* (1983) 346–349.
54 Gordon, J.W., and Ruddle, F.H., Mammalian gonadal determination and gametogenesis. Science *211* (1981) 1265–1271.
55 Gropp, A., Value of an animal model for trisomy. Virchows Arch *395* (1982) 117–131.
56 Guanti, G., Zuffardi, O., and Tiepolo, L., rDNA levels in infertile male carriers of Robertsonian translocations. Cytogenet. Cell Genet. *27* (1980) 162–167.
57 Guellaen, G., Casanova, M., Bishop, C., Geldworth, D., Andre, G., Gellous, M., and Weissenbach, J., Human XX males with Y single-copy DNA fragments. Nature *307* (1984) 172–173.
58 Hassold, T., Chiu, D., and Yamane, J.A., Parental origin of autosomal trisomies, Ann. hum. Genet. *48* (1984) 1–16.
59 Hassold, T., Quillen, S.D., and Yamane, J.A., Sex ratio in spontaneous abortions. Ann. hum. Genet. *47* (1983) 39–47.
60 Hassold, T., Jacobs, P., Kline, J., Stein, Z., and Warburton, D., Effect of maternal age on autosomal trisomies. Ann. hum. Genet. *44* (1980) 29–36.
61 Højager, B., Peters, H., Byskov, A.G., and Faber, M., Follicular development in ovaries of children with Down's syndrome. Acta paediat. scand. *67* (1978) 637–643.
62 Holm, P.B., and Rasmussen, S.W., Human meiosis. I. The human pachytene karyotype analysed by three dimensional reconstructions of the synaptonemal complex. Carlsberg Res. Commun. *42* (1977) 283–323.
63 Holm, P.B., and Rasmussen, S.W., Human meiosis. III. Electron microscopical analysis of chromosome pairing in an individual with a balanced translocation 46, XY, t(5p-;22p+). Carlsberg Res. Commun. *43* (1978) 329–350.
64 Holm, P.B., and Rasmussen, S.W., Human meiosis, V. Substages of pachytene in human spermatogenesis. Carlsberg Res. Commun. *48* (1983) 351–383.
65 Holm, P.B., and Rasmussen, S.W., Human meiosis. VI. Crossing-over in human spermatocytes. Carlsberg Res. Commun. *48* (1983) 385–413.
66 Holm, P.B., and Rasmussen, S.W., Human meiosis. VII. Chiasma formation in human spermatocytes. Carlsberg Res. Commun. *48* (1983) 415–456.
67 Holm, P.B., Rasmussen, S.W., and von Wettstein, D., The possible contribution of electron microscopy to the understanding of the mechanism of nondisjunction in man. Mut. Res. *61* (1979) 115–119.
68 Hook, E.B., Rates of chromosome abnormalities at different maternal ages. Obstet. Gynec. *58* (1981) 282–285.
69 Hook, E.B., Down syndrome rates and relaxed selection at older maternal ages. Am. J. hum. Genet. *35* (1983) 1307–1313.
70 Hotta, Y., and Stern, H., A DNA-binding protein in meiotic cells in *Lilium*. Devl Biol. *26* (1971) 87–99.
71 Hotta, Y., and Stern, H., DNA unwinding protein from meiotic cells of *Lilium*. Biochemistry *17* (1978) 1872–1880.
72 Hotta, Y., Chandley, A.C., and Stern, H., Meiotic crossing-over in lily and mouse. Nature *269* (1977) 240–242.
73 Hultén, M., and Lindsten, J., The behaviour of structural aberrations at male meiosis; information from man, in: Human Population Cytogenetics. Eds P.A. Jacobs, W.H. Price and P. Law. Pfizer Medical Monographs No. 5. Edinburgh University Press, Edinburgh 1970.
74 Hultén, M., and Lindsten, J., Cytogenetic aspects of human male meiosis, in: Advances in Human Genetics, vol. 4, pp. 327–387. Eds H. Harris and K. Hirschhorn. Plenum Press, New York 1973.
75 Hultén, M., and Pearson, P.L., Fluorescent evidence for spermatocytes with two Y chromosomes in an XYY male. Ann. hum. Genet. *34* (1971) 273–276.
76 Hungerford, D.A., Mellman, W.J., Balaban, G.B., LaBadie, G.U., Messatzzia, L.R., and Haller, G., Chromosome structure and function in man. III. Pachytene analysis and identification of the supernumerary chromosome in a case of Down's syndrome (mongolism). Proc. natn. Acad. Sci. USA *67* (1970) 221–224.
77 Jacobs, P.A., and Hassold, T.J., The origin of chromosome abnormalities in spontaneous abortions, in: Human Embryonic and Fetal Death, pp. 289–298. Eds I.H. Porter and E.B. Hook. Academic Press, New York 1980.

78 Jacobs, P.A., Melville, M., Ratcliffe, S., Keay, A.J., and Syme, J., A cytogenetic survey of 11,680 newborn infants. Ann. hum. Genet. *37* (1974) 359–376.

79 Jacobs, P.A., Harnden, D.G., Buckton, K.E., Court Brown, W.M., King, M.J., McBride, J.A., Macgregor, T.N., and Maclean, N., Cytogenetics studies in primary amenorrhoea. Lancet *i* (1961) 1183–1188.

80 Johannisson, R., Gropp, A., Winking, H., Coerdt, W., Rehder, H., and Swinger, E., Down's syndrome in the male. Reproductive pathology and meiotic studies. Hum. Genet. *63* (1983) 132–138.

81 Joseph, A.M., Gosden, J.R., and Chandley, A.C., Estimation of aneuploidy levels in human spermatozoa using chromosome specific probes and in situ hybridisation. Hum. Genet. *66* (1984) 234–238.

82 Kierszenbaum, A.L., and Tres, L.L., Transcription sites in spread meiotic prophase chromosomes from mouse spermatocytes. J. Cell Biol. *63* (1974) 923–925.

83 King, C.R., Magenis, E., and Bennett, S., Pregnancy and the Turner syndrome. Obstet. Gynec. *52* (1978) 617–624.

84 Kjessler, B., Chromosomal constitution and male reproductive failure, in: Male Fertility and Sterility, pp. 231–247. Eds R.E. Mancini and L. Martini. Academic Press, New York 1974.

85 Laurent, C., Chandley, A.C., Dutrillaux, B., and Speed, R.M., The use of surface spreading in the pachytene analysis of a human t(Y;17) reciprocal translocation. Cytogenet. Cell Genet. *33* (1982) 312–318.

85a Laurie, D.A., Palmer, R.W., and Hultén, M.A., Studies on chiasma frequency and distribution in two fertile men carrying reciprocal translocations; one with a t(9;10) karyotype and one with a t(Y;10) karyotype. Hum. Genet. *68* (1984) 235–247.

86 Léonard, A., and Deknudt, Gh., Etude cytologique d'une translocation chromosome Y- autosome chez la souris. Experientia *25* (1969) 876–877.

87 Lifschytz, E., and Lindsley, D.L., The role of X-chromosome inactivation during spermatogenesis. Proc. natn. Acad. Sci. USA *69* (1972) 182–186.

88 Lindsten, J., Marsk, L., Berglund, K., Iselius, L., Ryman, N., Anneren, G., Kjessler, B., Mitalman, F., Nordenson, I., Wahlström, J., and Vejlens, L., Incidence of Down's syndrome in Sweden during the years 1968–1977, in: Trisomy 21, pp. 195–210. Eds G.R. Burgio, M. Fraccaro, L. Tiepolo and U. Wolf. Springer-Verlag, Heidelberg 1981.

88a Luciani, J.M., Guiachaoua, M.R., Mattei, A., and Morazzani, M.R., Pachytene analysis of a man with a 13q;14q translocation and infertility. Behaviour of the trivalent and nonrandom association with the sex vesicle. Cytogenet. Cell Genet. *38* (1984) 14–22.

89 Lyon, M.F., Sex chromosome activity in germ cells, in: Physiology and Genetics of Reproduction, Part A, pp. 63–71. Eds E.M. Coutinho and F. Fuchs. Plenum Press, New York 1974.

90 Lyon, M.F., and Meredith, R., Autosomal tranlocations causing male sterility and viable aneuploidy in the mouse. Cytogenetics *5* (1966) 335–354.

91 McIlree, M.E., Selby-Tulloch, W., and Newsam, J.E., Studies on human meiotic chromosomes from testicular tissue. Lancet *i* (1966) 679–682.

92 McIlree, M.E., Price, W.H., Court Brown, W.M., Selby Tulloch, W., Newsam, J.E., and Maclean, N., Chromosome studies on testicular cells from 50 subfertile men. Lancet *ii* (1966) 69–71.

93 McLaren, A., Does the chromosomal sex of a mouse germ cell affect its development? in: Current Problems in Germ Cell Differentiation, pp. 225–240. Eds A. McLaren and C.C. Wylie. Cambridge University Press, Cambridge 1983.

94 McLaren, A., Chandley, A.C., and Kofman-Alfaro, S., A study of meiotic germ cells in the gonads of foetal mouse chimaeras. J. Embryol. expl Morph. *27* (1972) 515–524.

95 Madan, K., Hompes, P.G.A., Schoemaker, J., and Ford, C.E., X-autosome translocation with a breakpoint in Xq22 in a fertile woman and her 47, XXX infertile daughter. Hum. Genet. *59* (1981) 290–296.

96 Martin, R.H., Balkan, W., Burns, K., Rademaker, A.W:, Lin, C.C., and Rudd, N.L., The chromosome constitution of 1000 human spermatozoa. Hum. Genet. *63* (1983) 305–309.

97 Meyer, W.J., Migeon, B.R., and Migeon, C.J., Locus on human X-chromosome for dihydrotestosterone receptor and androgen insensitivity. Proc. natn. Acad. Sci. USA *72* (1975) 1469–1472.

98 Mikamo, K., Aguercif, M., Hazeghi, P., and Martin-du-Pain, R., Chromatin-positive Klinefelter's syndrome: a quantitative analysis of spermatogonial deficiency at 3, 4 and 12 months of age. Fert. Steril. *19* (1968) 731-739.

99 Mikkelsen, M., Hallberg, A., and Poulsen, H., Maternal and paternal origin of extra chromosome in trisomy 21. Hum. Genet. *32* (1976) 17–21.

100 Mikkelsen, M., Poulsen, H., Grinsted, J., and Lange, A., Non-disjunction in trisomy 21. Study of chromosomal heteromorphisms in 110 families. Ann. hum. Genet. *44* (1980) 17–28.

101 Miklos, G.L.G., Sex chromosome pairing and male fertility. Cytogenet. and Cell Genet. *13* (1974) 558–577.

102 Miller, J.F., Williamson, E., Glue, J., Gordon, Y.B., Grudzinskas, J.G., and Sykes, A., Fetal loss after implantation. Lancet *ii* (1980) 554–556.

103 Mittwoch, U., Mahadevaiah, S., and Olive, M.B., Retardation of ovarian growth in male-sterile mice carrying an autosomal translocation. J. med. Genet. *18* (1981) 414-417.

104 Moses, M.J., Microspreading and the synaptonemal complex in cytogenetic studies, in: Chromosomes Today, vol. 6, pp. 71–82. Eds A. de la Chapelle and M. Sorsa. Elsevier/North Holland, Amsterdam 1977.

105 Moses, M.J., New cytogenetic studies on mammalian meiosis, in: Animal Models in Human Reproduction, pp. 169–190. Eds M. Serio and L. Martini. Raven Press, New York 1980.

106 Moses, M.J., Counce, S.J., and Paulson, D.F., Synaptonemal complex complement of man in spreads of spermatocytes, with details of the sex chromosome pair. Science *187* (1975) 363–365.

107 Moses, M.J., Poorman, P.A., Roderick, T.H., and Davisson, M.T., Synaptonemal complex analysis of mouse chromosomal rearrangements. IV. Synapsis and synaptic adjustment in two paracentric inversions. Chromosoma (Berl.) *84* (1982) 457–474.

108 Nordensen, I., Population studies in northern Sweden. IX. Incidence of Down's syndrome by time, region and maternal age. Hereditas *91* (1979) 257–262.

109 Pearson, P.L., and Bobrow, M., Definitive evidence for the short arm of the Y chromosome associating with the X chromosome during meiosis in the human male. Nature *226* (1970) 959–961.

110 Peters, H., Byskov, A.G., and Grinsted, J., The development of the ovary during childhood in health and disease, in: Functional Morphology of the Human Ovary, pp. 26–34. Ed. J.R.T. Coutts. M.T.P. Press Ltd, Lancaster 1981.

111 Polani, P.E., Pairing of X and Y chromosomes, non-inactivation of X-lined genes, and the maleness factor. Hum. Genet. *60* (1982) 207–211.

112 Rappold, G.A., Cremer, T., Cremer, C., Back, W., Bogenberger, J., and Cooke, H.J., Chromosome assignment of two cloned DNA probes hybridizing predominantly to human sex chromosomes. Hum. Genet. *65* (1984) 257–261.

113 Rasmussen, S.W., and Holm, P.B., Human meiosis. II Chromosome pairing and recombination nodules in human spermatocytes. Carlsberg Res. Commun. *43* (1978) 275–327.

114 Rasmussen, S.W., and Holm, P.B., Human meiosis. IV. The elimination of synaptonemal complex fragments from metaphase I bivalents of human spermatocytes. Carlsberg Res. Commun. *43* (1979) 423–438.

115 Rasmussen, S.W., and Holm, P.B., Mechanics of meiosis. Hereditas *93* (1980) 187–216.

116 Read, S.G., The distribution of Down's syndrome. J. ment. Defic. Res. *26* (1982) 215–227.

117 Reyes, F.I., Koh, K.S., and Faiman, C., Fertility in women with gonadal dysgenesis. Am. J. Obstet. Gynec. *126* (1976) 668–670.

117a Rosenmann, A., Wahrman, J., Richler, C., Voss, R., Persitz, A., and Goldman, B., Meiotic association between the XY chromosomes and unpaired autosomal elements as a cause of human male sterility. Cytogenet. Cell Genet. *39* (1985) 19–29.

118 Russell, P., and Altschuler, F., The ovarian dysgenesis of trisomy 18. Pathology *7* (1975) 149–155.

119 Sarto, G.E., Therman, E., and Patau, K., X inactivation in man: a woman with t(Xq-;12q+). Am. J. hum. Genet. *25* (1973) 262–270.

120 Schempp, W., and Meer, B., Cytologic evidence for three human X-chromosomal segments escaping inactivation. Hum. Genet. *63* (1983) 171–174.

121 Schreinemachers, D.M., Cross, P.K., and Hook, E.B., Rates of trisomies 21, 18, 13 and other chromosome abnormalities in about 20,000 prenatal studies compared with estimated rates in live births. Hum. Genet. *61* (1982) 318–324.

122 Searle, A.G., The genetics of sterility in the mouse, in: Genetic Control of Gamete Production and Function, pp. 93–114. Eds P.G. Crosignani and B.L. Rubin. Academic Press/Grune and Stratton 1982.

123 Simpson, J.L., Abnormal sexual differentiation in humans. A. Rev. Genet. *16* (1982) 193–224.

124 Singh, R.P., and Carr, D.H., The anatomy and histology of XO human embryos and fetuses. Anat. Rec. *155* (1966) 369–383.
125 Skakkebaek, N., Hultén, M., and Philip, J., Quantification of human seminiferous epithelium. IV. Histological studies in 17 men with numerical and structural autosomal aberrations. Acta path. microbiol. scand. Sect. A *81* (1973) 112–124.
126 Skakkebaek, N.E., Hultén, M., Jacobsen, P., and Mikkelsen, M., Quantification of human seminiferous epithelium. II. Histological studies in eight 47,XYY men. J. Reprod. Fert. *32* (1973) 391–401.
127 Smith, A., Fraser, I.S., and Elliott, G., An infertile male with balanced Y;19 translocation. Review of Y; autosome translocations. Annls Génét. *22* (1979) 189–194.
128 Smith, G.F., and Berg, J.M., Down's anomaly. 2nd edn. Churchill Livingstone Edinburgh, London, New York 1976.
129 Solari, A.J., Synaptonemal complexes and associated structures in microspread human spermatocytes. Chromosoma *81* (1980) 315–337.
130 Solari, A.J., and Tres, L., The three dimensional reconstruction of the XY chromosomal pair in human spermatocytes. J. Cell Biol. *45* (1970) 43–53.
131 Speed, R.M., Meiotic configurations in female trisomy 21 foetuses. Hum. Genet. *66* (1984) 176–180.
131a Speed, R.M., The prophase stages in human foetal oocytes studied by light and electron microscopy. Hum. Genet. *69* (1985) 69–75.
131b Speed, R.M., Oocyte development in XO foetuses of man and mouse: The possible role of heterologous X-chromosome pairing in germ cell survival. Chromosoma, 1986 in press.
132 Stern, H., Chromosome organization and DNA metabolism in meiotic cells, in: Chromosomes Today, vol.7, pp.94–103. George Allen and Unwin 1981.
133 Stern, H., and Hotta, Y., Biochemistry of meiosis. Phil. Trans R. Soc. Lond. B *277* (1977) 277–294.
134 Stern, H., and Hotta, Y., The organization of DNA metabolism during the recombinational phase of meiosis with special reference to humans. Molec. cell. Biochem. *29* (1980) 145–158.
135 Summitt, R.L., Tipton, R.E., Wilroy, R.S., Martens, P.R., and Phelan, J.P., X-autosome translocations: A review. Birth Defects: Original Article Series, vol.XIV, No.6C, pp.219–247. The National Foundation 1978.
136 Thompson, H., Melnyk, J., and Hecht, F., Reproduction and meiosis in XYY. Lancet *2* (1967) 831.
137 Thomson, E., Fletcher, J., Chandley, A.C., and Kučerová, M., Meiotic and radiation studies in four oligochiasmatic men. J. med. Genet. *16* (1979) 270–277.
138 Tiepolo, L., and Zuffardi, O., Localization of factors controlling spermatogenesis in the non-fluorescent portion of the human Y chromosome long arm. Hum. Genet. *34* (1976) 119–124.
139 Tiepolo, L., Zuffardi, O., Fraccaro, M., and Giarola, A., Chromosome abnormalities and male infertility, in: Oligozoospermia: Recent Progress in Andrology, pp.233–245. Eds G. Frajese, E.S.E. Hafez, C. Conti and A. Fabbrini. Raven Press, New York 1981.
140 Tres, L.L., Nucleolar RNA synthesis of meiotic prophase spermatocytes in the human testis. Chromosoma *53* (1975) 141–151.
141 Uchida, I., Epidemiology of mongolism: The Manitoba study, in: Down's Syndrome (Mongolism), pp.361–369. Ed. V. Apgar. Ann. N.Y. Acad. Sci. *171* (1970).
142 van der Linden, A.G.J.M., Pearson, P.L., and Kamp, J.J.P., van de, Cytological assessment of meiotic exchange in a human male with a pericentric inversion of chromosome No.4. Cytogenet. Cell Genet. *14* (1975) 126–139.
143 Wachtel, S.S., and Selden, J.R., The X chromosome in abnormal sexual development, in: Cytogenetics of the Mammalian X Chromosome, Part B: X Chromosome Anomalies and their Clinical Manifestations, pp.87–114. Alan R. Liss, New York 1983.
144 Wallace, B.M.N., and Hultén, M.A., Triple chromosome synapsis in oocytes from a human foetus with trisomy 21. Ann. hum. Genet. *47* (1983) 271–276.
145 Warburton, D., and Fraser, F.C., Spontaneous abortion risks in man: data from reproductive histories collected in Medical Genetics Unit. Am. J. hum. Genet. *16* (1964) 1–27.
146 Warburton, D., Stein, Z., and Kline, J., In utero selection against fetuses with trisomy. Am. J. hum. Genet. *35* (1983) 1059–1063.
147 Warburton, D., Stein, Z., Kline, J., and Susser, M., Chromosome abnormalities in spontaneous abortion: data from the New York City study, in: Human Embryonic and Fetal Death, pp.261–288. Eds I.H. Porter and E.B. Hook. Academic Press, New York 1980.

0014-4754/86/101109-09$1.50 + 0.20/0
© Birkhäuser Verlag Basel, 1986

Developmental genetics

by C.J. Epstein[1]

Departments of Pediatrics and of Biochemistry and Biophysics, University of California, San Francisco (California 94143-0106, USA)

Summary. Of particular concern to the human geneticist are the effects of genetic abnormalities on development. To gain an understanding of these effects it is necessary to engage in a reciprocal process of using knowledge of normal developmental events to elucidate the mechanisms operative in abnormal situations and then of using what is learned about these abnormal situations to expand our understanding of the normal. True developmental genes have not been described in man, although it is likely that they exist, but many developmental abnormalities are ascribable to mutations in genes coding for enzymes and structural proteins. Some of these even produce multiple malformation syndromes with dysmorphic features. These situations provide a precedent for asserting that not only monogenic developmental abnormalities, but also abnormalities resulting from chromosome imbalance must ultimately be explicable in molecular terms. However, the major problem confronted by the investigator interested in the pathogenesis of any of the chromosome anomaly syndromes is to understand how the presence of an extra set of normal genes or the loss of one of two sets of genes has an adverse effect on development. Several molecular mechanisms for which limited precedents exist may be considered on theoretical grounds. Because of the difficulties in studying developmental disorders in man, a variety of experimental systems have been employed. Particularly useful has been the mouse, which provides models for both monogenic and aneuploidy produced abnormalities of development. An example of the former is the mutation oligosyndactylism which in the heterozygous state causes oligosyndactyly and in the homozygous state causes early embryonic mitotic arrest. All whole arm trisomies and monosomies of the mouse can be produced experimentally, and of special interest is mouse trisomy 16 which has been developed as an animal