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Genetically Determined Asynapsis, Spermatogenic Degeneration, and Infertility in Men

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SUMMARY

We report a family in which azoospermia and infertility affected two sibs whose parents were first cousins once removed. Meiotic cells of the proband, who had the chromosomal complement of a normal male (46,XY), exhibited asynapsis, defective synaptonemal complex (SC) formation, chiasma failure, and degeneration of prophase spermatocytes with asynapsis. Based on these observations, we suggest that the meiotic abnormalities and infertility in this family comprise a trait with an autosomal recessive mode of inheritance. Review of published cases of infertile men with normal chromosomal complements and disturbed meiosis suggests that genetically determined asynapsis and desynapsis similar to that established in plant and insect species also occur in humans. In humans, asynapsis appears to be inherited as an autosomal recessive. The mode of inheritance of desynapsis is not clear; X-linked recessive or autosomal dominant has been suggested in one family. Studies by us and by others reported in the literature suggest that the mode of action of genes that affect synapsis and cause a reduction in the numbers of visible chiasmata at diakinesis is dissimilar to that of the action of genes that cause defective meiotic recombination, defective repair of induced damage to DNA in somatic cells, and chromosome instability.

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INTRODUCTION

The discovery by Gowen and Gowen [1] in 1917 of the *c(3)G* gene in *Drosophila*, which causes suppression of crossing over and nondisjunction at meiosis in females, marked the beginning of genetic approaches to the analysis of meiosis [2, 3]. Genetic control of meiosis has since been studied extensively in yeast, *Neurospora*, higher plants, and *Drosophila* [4]. Genetically determined meiotic nondisjunction has recently been reported in the nematode worm *Caenorhabditis elegans* [5]. While the remarkable morphological similarity of the meiotic process throughout the eukaryotic phyla predicts a genetic control of mammalian meiosis as well, few mutations have been recognized so far. In the mouse, a presumptive recessive gene causing univalent formation at diakinesis and spermatogenic arrest [6] has been reported. In humans, meiosis has been found to be abnormal in occasional instances of phenotypically and chromosomally normal men studied for infertility [7–15]. Parental consanguinity was present in two of the 14 such cases reported [8, 12] (table 1). An additional two men had affected family members [12, 15]. These observations suggest that abnormal meiosis in humans might also have a genetic basis [10, 12, 15].

We report here a family in which azoospermia and infertility affected two sibs. The meiotic cells of the normally developed proband, who had a normal (46,XY) chromosomal complement, exhibited defective chromosome pairing and SC formation, chiasma failure, pachytene spermatocyte degeneration, and azoospermia. The many consanguineous marriages in this family (fig. 1) suggest that meiotic abnormalities seen in the proband and the infertility of the sibs comprise a trait with an autosomal recessive mode of inheritance.

ASCERTAINMENT AND CLINICAL HISTORY

The proband (VI.82 in fig. 1), a healthy and normally developed 36-year-old Iranian, sought evaluation of his infertility. He had been married for 4 years. Contraception was practiced for the first 6 months of marriage and discontinued thereafter. His normally developed wife had never conceived in spite of the couple's desire to have children. He had not been subjected to unusual exposure to chemicals or radiation. He had normal libido; his external genitalia were normally developed, and his body hair was masculine in distribution. Hormonal studies performed by radioimmunoassay [16, 17] revealed a normal male endocrine profile with normal levels of follicle-stimulating hormone (17 mIU/ml), luteinizing hormone (16 mIU/ml), serum testosterone (486 ng%), thyroid-stimulating hormone (0.4 μU/ml), thyroxine (10 μg/dl), triiodothyronine (170 ng/dl), and serum prolactin (5.6 ng/ml).

He was reported to be azoospermic after a semen examination performed in Iran. An examination performed at The New York Hospital in October, 1978, revealed a sperm count of less than 1 million/cc; compared with counts of over 20 million/cc found in fertile men [18], his semen was nearly azoospermic. A testicular biopsy was performed in May, 1979, for histological evaluation and cytogenetic studies. In the hematoxylin and eosin (H&E)-stained sections, the tubules varied with reference to the amount and type of spermatogenesis present in them. An occasional tubule showed patches of normal-appearing spermatogenesis (fig. 2). The vast majority of tubules, however, showed abnormal spermatogenesis, with most germ cells in the early prophase stage of meiosis (fig. 3). In addition, many of these cells had a vacuolated cytoplasm and were degenerating. In many tubules, the degenerating germ cells had sloughed off from the tubule wall (fig. 4). Sertoli and Leydig cells were normal in frequency and appearance.

The proband's 34-year-old brother (VI.83, fig. 1) was also infertile in 3 years of marriage. His semen, examined in Iran, was reported to have a low sperm count.

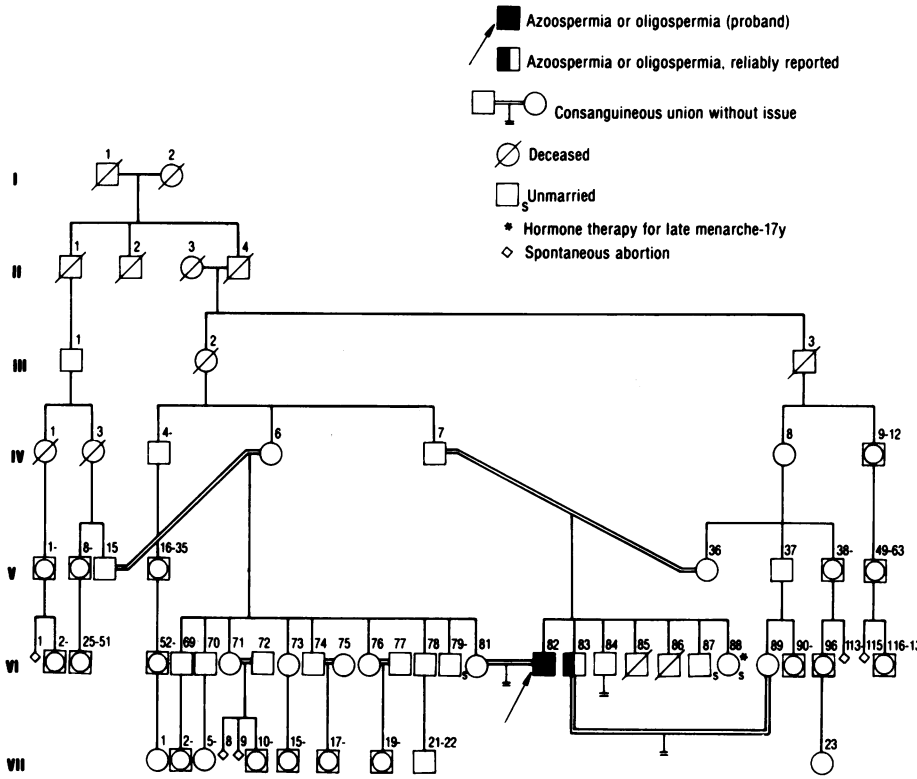


FIG. 1.—Pedigree of family with consanguinity, azoospermia, and male infertility. Proband, with asynaptic meiosis and spermatogenic degeneration, is indicated by *arrow*.

MATERIALS AND METHODS

Mitotic chromosome preparations were made from phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes and cultured dermal fibroblasts of the proband following conventional methods. His chromosomal complement was determined from G-banded preparations. A chromosome breakage study was performed on orcein-stained metaphases from fibroblast cells. Sister chromatid exchange (SCE) frequency was determined in PHA-stimulated lymphocytes after culture in bromodeoxyuridine (BrdU)-containing medium.

Meiotic chromosome preparations were made from testicular biopsy specimens from the proband following methods previously described [19, 20]. A variety of hypotonic treatments was employed: 1% sodium citrate for 10 min, 30 min, and 60 min; and 0.7% sodium citrate for 40 min. Preparations were stained in one of two ways: with a 4% Giemsa solution, pH 6.8, for 5–10 min or with carbol fuchsin [21]. For the study of SC, silver staining was applied by treating the preparations with borate buffer, pH 9.0, for 20–30 min followed by incubation in a 50% silver nitrate solution for 24–84 hrs in a moist chamber at 50°C [20]. The preparations were counterstained with 1% Giemsa for two min, rinsed in distilled water, and air-dried.

RESULTS

Somatic Cells

The chromosomal complement of the proband, as determined by G-banding of PHA-stimulated blood lymphocytes, was that of a normal male, 46,XY. A study of

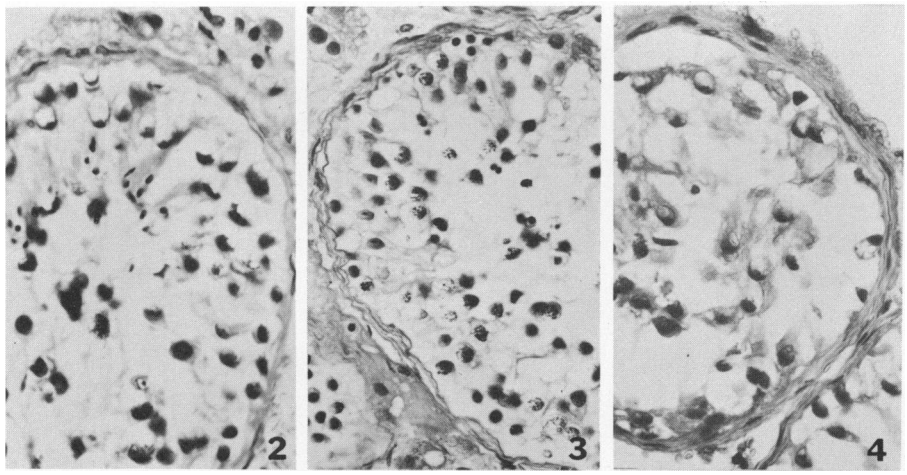
TABLE 1

FAMILY HISTORY, SEMEN ANALYSIS, SPERMATOCYTE MATURATION, AND MEIOSIS IN 16 INFERTILE MEN REPORTED TO SHOW ASYNAPSIS OR DESYNAPSIS DURING MEIOSIS

CASE NO.	FAMILY HISTORY		SEMEN	SPERMATOGENESIS ARRESTED AT	MEIOSIS	
	Parental consanguinity	Other family members affected			Zygotene-Pachytene	Diakinesis-Metaphase I
1 [7]	...	...	Azoospermic	Primary spermatocyte	...	Desynapsis, very low chiasma frequency
2 [8]	Yes	One sister infertile	Azoospermic	Primary spermatocyte	Normal	Low chiasma frequency (mean of 39.2/cell), multivalents, univalents, fragments
3 [8]	No	No	Azoospermic	Primary spermatocyte	Normal	Low chiasma frequency (mean of 41.5/cell), multivalents, univalents, fragments
4 [9]	No	No	Oligo-, astheno-, terato-, and necrospermic	No spermatogenic arrest	Normal	Desynapsis, polyploid spermatocytes
5 [10]	No	No	Azoospermic	Primary spermatocyte	Asynapsis, absence of SV, and abnormal SC	Very low chiasma frequency
6 [11]	...	...	...	Primary spermatocyte	Asynapsis	Metaphase breakdown
7 [12]	Yes	...	...	Prophase I	Asynapsis and absent SV in 15% of spermatocytes	Low chiasma frequency (mean of 21.5/cell)
8 [12]	...	Two brothers and one of two sisters infertile	...	Primary spermatocyte	Asynapsis, and absence of SV in 100% of cells, abnormal SC	Very low chiasma frequency (mean of 3.1/cell), univalents

TABLE 1 (continued)

Case no.	Family history: Parental consanguinity	Family history: Other family members affected	Semen	Spermatogenesis arrested at	Meiosis: Zygotene-Pachytene	Meiosis: Diakinesis-Metaphase I
9 [13]	...	No	Oligo-, astheno-, and teratozoospermic	Spermatid	Normal	20% cells with low chiasma frequency, desynapsis
10 [13]	...	No	Poly-astheno-, and teratozoospermic	...	Abnormal	Desynapsis, univalents
11 [14]	...	No	Oligospermic	No spermatogenic arrest	Normal	Low chiasma frequency (mean of 40.6/cell), univalents
12 [14]	...	No	Oligospermic	No spermatogenic arrest	Normal	Low chiasma frequency (mean of 39.3/cell), univalents
13 [14]	...	No	Oligospermic	Primary spermatocyte	Normal	Low chiasma frequency (mean of 28.1/cell), univalents, degeneration
14 [14]	...	No	Azoospermic	Primary spermatocyte	Predominantly normal. One or two pachytene cells with pairing failure	Desynapsis, univalents, degeneration
15 [15]	No	Maternal uncle and mother's sister's son infertile	Oligospermic	Primary spermatocyte	Normal	Desynapsis, univalents, degeneration
16 [This study]	Yes	One brother infertile	Azoospermic	Primary spermatocyte	Asynapsis, absence of SV in 78% of cells, abnormal SC	Slight overall reduction of chiasma frequency in cells with bivalent pairing (mean of 47.08/cell), univalents



FIGS. 2–4. —Sections of seminiferous tubules of proband illustrating testicular histology described in ASCERTAINMENT AND CLINICAL HISTORY. *Figure 2*, Tubule with a patch of normal-appearing spermatogenesis. Spermatocytes in meiosis and spermatids in different stages of maturation are present; *figure 3*, tubule with spermatocytes predominantly in early prophase of meiosis; *figure 4*, tubule with degenerating germ cells that had sloughed off from its wall. H&E stain.

100 orcein-stained metaphases from cultured dermal fibroblasts did not reveal evidence of increased chromosome breakage. His blood lymphocytes had a mean of 7.6 SCE per cell, which is similar to that of normals studied in our laboratory.

Germinal Cells

Meiotic preparations exhibited an abundance of spermatogonial cells in mitosis and unusually large numbers of spermatocytes in early prophase. In 206 randomly selected germ cells evaluated for maturation and stage of division, the following frequencies were noted: spermatogonial cells at metaphase, 12.1%; spermatocytes at leptotene to pachytene, 76.7%; spermatocytes at diakinesis to metaphase I, 10.2%; spermatocytes at metaphase II, 0.0%; and spermatids, 1.0%. In normal men, spermatogonial cells at metaphase and meiotic cells at first and second metaphases have been reported to occur at frequencies of 10.9%, 52.8%, and 36.4%, respectively [22]. Thus, the majority of the proband's spermatocytes were unable to progress beyond the pachytene stage. Chromosome numbers were determined in 61 spermatogonial mitoses (table 2). Of these, 4.9% had hypodiploid, 63.9% diploid, 27.9% hyperdiploid, and 3.3% tetraploid chromosome numbers. The hypodiploid cells are presumed to have arisen as a result of cell rupture during preparation. Chromosome arms were often seen separated at the centromeres and probably accounted for the hyperdiploid cells.

In the carbol fuchsin- and Giemsa-stained preparations, early prophase cells exhibited striking pairing failure and degeneration. The extent of pairing varied from completely paired to completely unpaired homologs. A sex vesicle (SV) was present in only a minority of cells. The severity of pairing failure was evaluated in 100 randomly selected Giemsa-stained cells. In 22 cells, SVs were present and autosomes exhibited predominantly bivalent pairing; occasional unpaired regions were present in autosomes (fig. 5). In 38 cells, SVs were absent and autosomes exhibited moderate to severe

TABLE 2

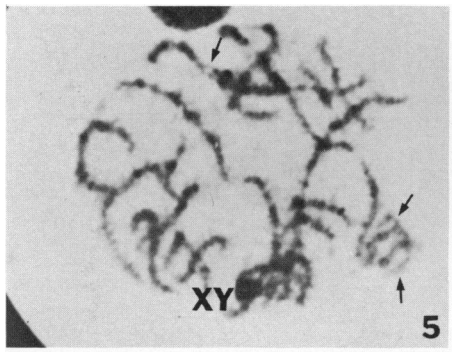
DISTRIBUTION OF CHROMOSOME NOS. IN 61 SPERMATOGONIAL MITOSES OF THE PROBAND

							Total no. cells
No. chromosomes per cell	< 46	46	47	48	49	92	
No. cells	3	39	7	8	2	2	61

pairing failure (figs. 6 and 7). In the remaining 40 cells, SVs were also absent and all autosomes were completely unpaired (fig. 8).

From the silver-stained preparations, cells were selected that exhibited chromosome pairing similar to the types described above, and the SCs in them were examined. Cells that had SVs and normal autosomal pairing also had SCs comparable to those seen in spermatocytes from normal individuals [23, 24] (fig. 9). In the cells that lacked SVs and in which the autosomes remained unpaired, silver-stained elements, interpreted by us as axial elements, were present in the autosomes (figs. 10 and 11). These were often discontinuous along the length of the chromosome (fig. 12). Abnormal SCs have been reported in electron microscope studies of asynaptic meiosis in two other men [10, 12]. Comparison of organization of SCs with synapsis in our preparations showed that the extent to which SCs were formed correlated well with the extent to which chromosomes were paired. Thus, the critical lesion in the meiosis of the proband is defective pairing, which in turn leads to defective SC formation. Many cells that lacked SCs and exhibited severe to complete asynapsis were seen to be degenerating. The chromosomes in these cells, when stained with Giemsa, appeared decondensed to a lightly stained chromatin (figs. 13–15). The discontinuity in the axial elements of autosomal univalents mentioned above probably represents an early stage in chromatin decondensation.

A proportion of cells exhibited univalent chromosomes at diakinesis and metaphase I (figs. 16 and 17). In addition, univalents underwent equational division as early as diakinesis. In 123 cells studied at these stages (table 3), 103 (83.7%) showed bivalent associations of autosomes. In 77 of these 103 cells, the sex chromosomes associated as bivalents; in 26, they remained as univalents. This 3:1 ratio of bivalent to univalent association of sex chromosomes is similar to that seen in spermatocytes from normal individuals studied in our laboratory and suggests that all of these 103 cells had SVs and autosomal pairing at pachytene. In the remaining 20 cells (16.3%), autosomal univalents were present and ranged in number from two to 36. In eight of the 20 cells with autosomal univalents, the sex chromosomes were associated as bivalents, suggesting that they also arose from pachytene cells with SVs. In the remaining 12 cells, the sex chromosomes were present as univalents. These latter cells exhibited as many as 36 univalents (table 3) and probably originated from pachytene cells with moderate to severe failure of pairing. When the entire group of 123 cells that did reach diakinesis and metaphase I was considered together, a predominantly bivalent pairing of autosomes was seen (mean of 21.2 bivalents per cell compared with the expected 22). Thus, in the proband, when a germ cell is able to reach diplotene and proceed further in meiosis, the chromosome pairing in it is more likely to be closer to normal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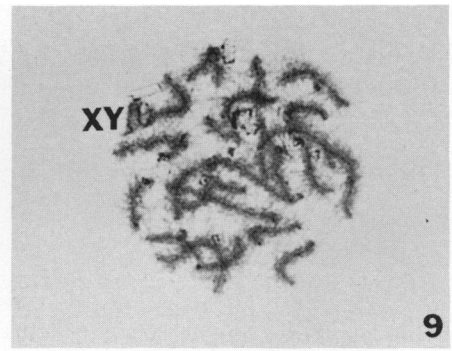
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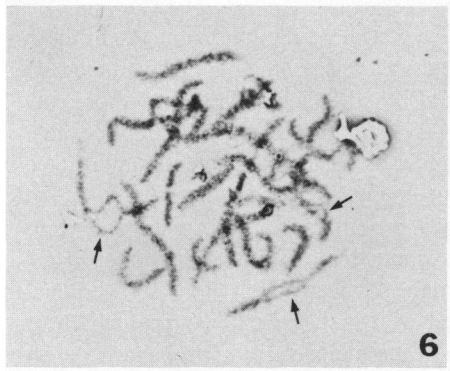
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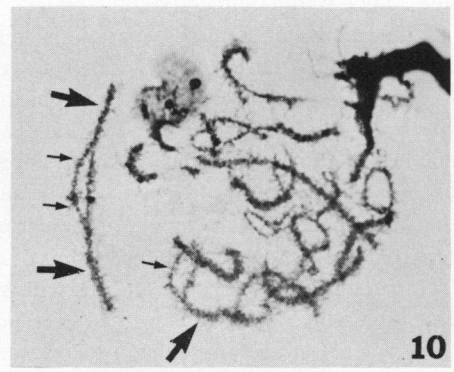
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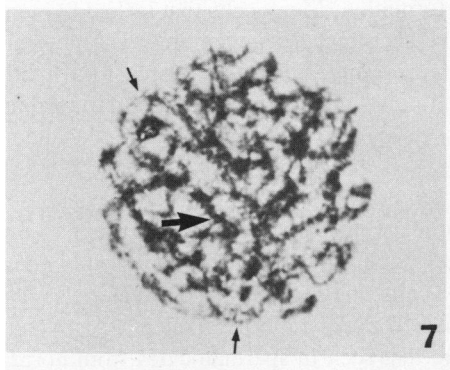
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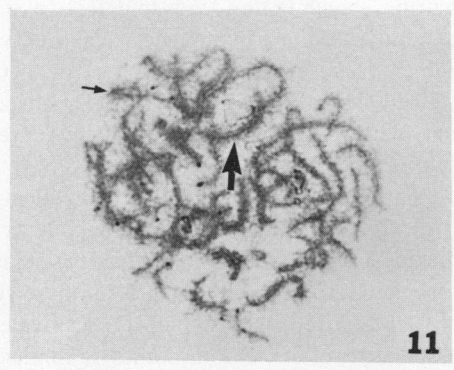
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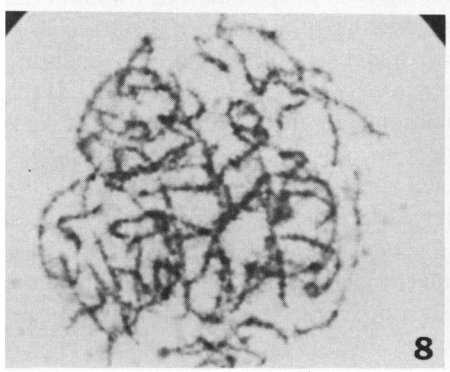
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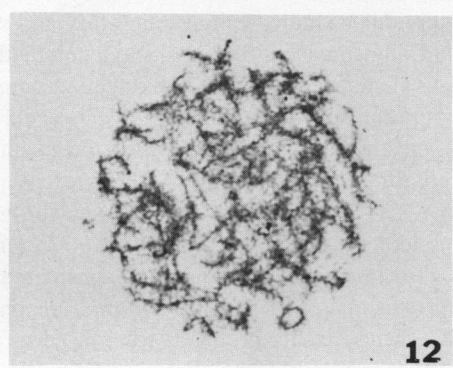
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than to abnormal. Cells that entered diakinesis presumably completed meiosis and gave rise to the few spermatozoa that were seen in the proband's ejaculate.

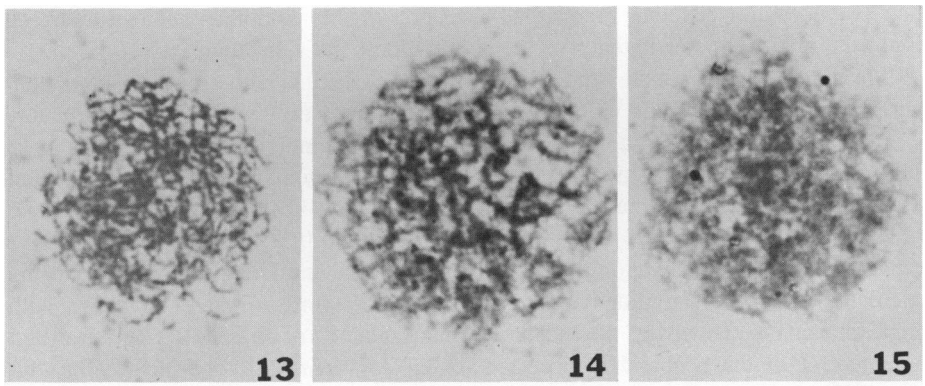
Chiasma frequencies were studied in 13 cells at diakinesis that exhibited bivalent pairing of autosomes. Cells with autosomal univalents were excluded from the study because chiasmata in them could not be ascertained unambiguously. In six of the 13 cells, the sex chromosomes associated as bivalents; in the remainder, they were present as univalents. The mean chiasma frequency per cell was 47.08 (range: 42–53) (table 4), which is only slightly lower than the values of 50.0 (range: 43–60) and 51.2 (range: 43–57) per cell reported in cells from normal individuals [25, 26]. (In the calculation of chiasma frequencies, XY associations were scored as bivalents with single chiasmata.) However, the mean chiasma frequency of all cells at diakinesis and metaphase I in the proband is expected to be less than 47.08 because cells with autosomal univalents have fewer chiasmata than those lacking univalents.

In normal men, the mean number of bivalents per cell with one, two, three, four, five, and six chiasmata was reported to be 3.3, 10.9, 5.6, 1.9, 0.4, and 0.03, respectively [26]. In the proband's cells, the mean number of bivalents per cell with one, two, three, and four chiasmata was 4.9, 12.9, 4.1, and 0.5, respectively; bivalents with five and six chiasmata were absent (table 4). This slight reduction in chiasma frequency in the proband's cells with normal pairing can probably be attributed to chiasma failure in the occasional unpaired regions present in pachytene cells with predominantly normal pairing. The effect of asynapsis and chiasma failure on chromosome disjunction at anaphase I could not be studied in detail because insufficient numbers of secondary spermatocytes were present in our preparations. The two encountered on eight slides had 26 and 28 chromosomes, respectively (fig. 18), indicating that abnormal disjunction did occur.

DISCUSSION

Genes that affect male fertility fall into two general categories. In the first are those that arrest spermatocyte maturation at different stages of development; they do not have an effect on the behavior of chromosomes during meiosis. The mouse mutations *white* (*W*) and *steel* (*Sl*) are probably the earliest acting of such genes [27]; in homozygous embryos, primordial germ cells fail to multiply between the eighth and twelfth days of fetal life and adult testes lack germ cells. The Sertoli-cell-only syndrome in humans, possibly an inherited disorder [28], most likely has a similar pathology. In *ameiotic* (*am*) [29], a recessive trait in maize, microspore mother cells do not enter meiosis, but

FIGS. 5–12. —Pachytene spermatocytes from air-dried meiotic preparations of seminiferous tubules from proband. *Figures 5–8*, Giemsa-stained cells exhibiting different degrees of asynapsis; *figure 5*, cell with SV and predominantly bivalent pairing of autosomes. Three unpaired regions are indicated by *arrows*; *figures 6–8*, cells that lack SVs and with moderate (*fig. 6*), severe (*fig. 7*), and complete (*fig. 8*) asynapsis. *Thick arrows* point to representative paired regions, *thin arrows* point to representative unpaired regions; *figures 9–12*, silver-stained cells with chromosomal pairing comparable to that present in cells in *figures 5–8*, respectively; *figure 9*, cell with normal X and Y axial elements and normal autosomal SCs; *figures 10 and 11*, cells with SCs in paired regions and axial elements in unpaired regions. *Thick arrows* point to representative SC, *thin arrows* point to representative axial elements; *figure 12*, cell completely lacking SCs. Axial elements present but discontinuous in many chromosomal regions.



FIGS. 13–15.—Chromatin decondensation in degenerating spermatocytes with asynaptic prophase. *Figure 13*, Cell with complete asynapsis; *figure 14*, cell in which chromatin decondensation, characterized by fuzzy and granular-appearing chromosomes, had set in; *figure 15*, cell in which only granular chromatin can be seen.

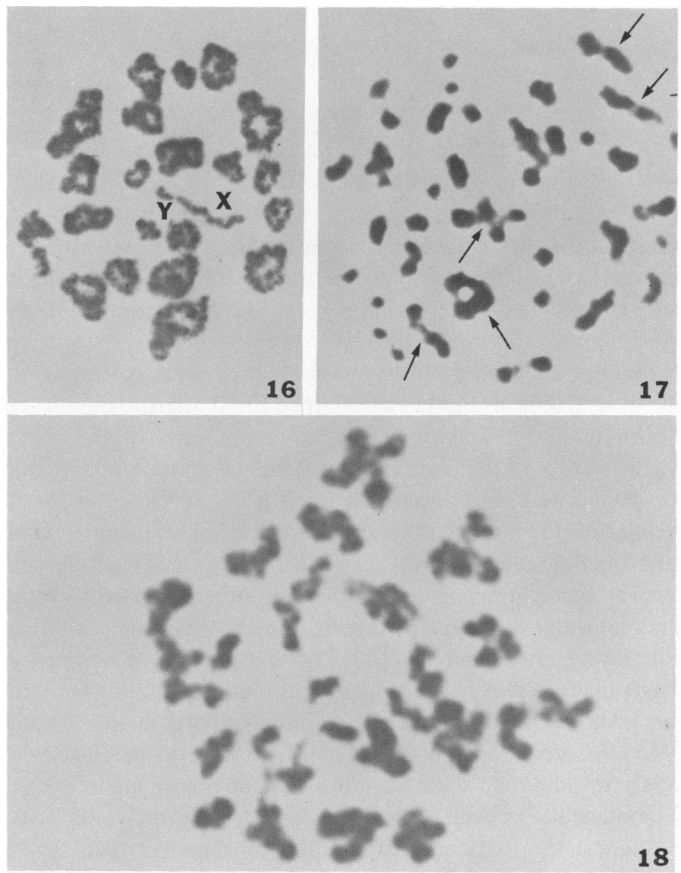
instead undergo a mitotic division and degenerate. A number of genes in maize and other plant species cause degeneration of the microsporocytes at different stages of development and, therefore, male sterility [30]. Among animal species, spermatogenic arrest leads to azoospermia in strains of guinea pig, mouse, Syrian hamster, and cattle [31]. In humans, arrest of spermatocyte maturation at different stages of development has been reported in healthy and normally developed men with normal karyotypes and meiosis [26, 32].

In the second category are genes that cause perturbations of meiosis. Their effect on fertility is neither obligate nor always related to the abnormal meiosis. These genes, which usually show a recessive expression, have been detected and studied extensively in *Drosophila*, maize, and other plant species [4, 30]. The majority of such genes affect meiosis I; genes affecting meiosis II are infrequent. Affected aspects of meiosis most often detected are chromosome pairing, crossing over, chiasma formation, and disjunction at anaphase I. Extensive genetic analysis has been made of *Drosophila* and *Neurospora* mutations that affect recombination, and detailed cytological analyses have been made of plant mutations that affect chromosome pairing and chiasma frequency.

A distinction is often made between genetically determined failure of synapsis at zygotene (asynapsis) and precocious separation of paired homologs at late pachytene (desynapsis); however, the terms asynapsis and desynapsis have not been used consistently in the literature. A number of genes labeled as *asynaptic* or *desynaptic* have been reported in plant species [4]. At the light microscope level, it is often difficult to distinguish between the two conditions as both lead to unpaired chromosomes at late pachytene and univalents at diakinesis and metaphase I. Recent electron microscope studies of SCs in genetically determined pairing failure have demonstrated that the two types can be distinguished from each other. In the asynaptic mutants in durum wheat (*as*) and *Drosophila* (*c(3)G* and *mei-W68*), only axial elements are present; central elements and SCs fail to form [33–35]. Asynapsis seen with the light

microscope in these mutants is, therefore, due to failure of homologs to come together and form SCs. On the other hand, in the tomato desynaptic mutants as_1, as_4, and as_b, initial pachytene pairing, as well as SC formation, is normal [36]. The variable pairing at later pachytene and subsequent stages of meiosis in these mutants is, therefore, due to precocious resolution of pairing.

In humans, asynaptic meiosis similar to that described in maize [37–40] and other organisms has been reported in four infertile males (case nos. 5–8 in table 1) prior to our study of meiosis in our proband. SC studies performed in three of these men, including the proband, showed abnormalities similar to those observed in the asynaptic mutants of wheat and *Drosophila* discussed above. Parental consanguinity in the case of one man (case no. 7 in table 1), presence of affected sibs in the case of another man (case no. 8 in table 1), and both parental consanguinity and an affected sib in the case of the proband of our family suggest that a mutation is responsible for the meiotic



FIGS. 16–18. —Diakinesis stage of meiosis in the proband; *figure 16*, normal cell with sex chromosomes associated end-to-end and autosomes paired as bivalents; *figure 17*, abnormal cell with one ring bivalent and four possible rod bivalents (*arrows*). Some univalents can be seen undergoing equational division. *Figure 18*, A secondary spermatocyte (one of two encountered in the study) with 28 chromosomes.

TABLE 3

CHROMOSOME ASSOCIATIONS IN 123 CELLS AT DIAKINESIS AND METAPHASE I FROM THE PROBAND

	TYPES OF CHROMOSOME ASSOCIATIONS			
	AUTOSOMES		SEX CHROMOSOMES	
NO. CELLS	Bivalents	Univalents	Bivalents	Univalents*
77	22	...	1	...
26	22	...	...	2
6	21	2	1	...
3	21	2	...	2
1	20	4	1	...
2	20	4	...	2
1	19	6	1	...
1	18	8	...	2
1	16	12	...	2
1	13	18	...	2
1	10	24	...	2
1	8	28	...	2
1	7	30	...	2
1	4	36	...	2
Mean/cell:	21.22	1.56	0.69	0.62

* Two half univalents (derived from equational division of a univalent) scored as one univalent.

abnormality and that the trait is inherited as an autosomal recessive. Degeneration of prophase spermatocytes, which is responsible for the azoo- and oligospermia of these men, is probably a semilethal effect of the gene on the spermatocytes that is unrelated to its effect on synapsis.

Desynaptic meiosis characterized by normal pachytene pairing and failure of chiasmata to form at diakinesis has been described in 10 infertile men (case nos. 1–4, 9, and 11–15 in table 1), making it the more common of the two anomalies. Unfortunately, SC studies of them are lacking. Parental consanguinity and an infertile sister were present in the case of one man (case no. 2 in table 1). In the family of another man (case no. 15 in table 1), male infertility was transmitted as an X-linked recessive or autosomal dominant trait. Clearly, SC studies and discovery of additional familial clusters are needed to clarify the nature and inheritance of desynapsis.

Although the molecular mechanisms involved in chromosome pairing and crossing over are rapidly being elucidated [41, 42], nothing is known at present about the biochemical basis of genetically determined perturbations in chromosome pairing. It has recently been shown that a number of recombination-defective mutants in yeast, *Neurospora*, and *Drosophila* have impaired ability to repair damage caused to DNA in somatic cells [4]. In addition, some of these *Drosophila* mutants exhibit increased frequency of spontaneous as well as mutagen-induced chromosome instability [43]. These studies suggest the existence of common biochemical pathways for meiotic recombination, DNA repair, and maintenance of chromosome stability. Using somatic cells of oligochiasmatic men, several studies have attempted to evaluate one or more of the parameters of spontaneous and mutagen-induced chromosome breakage, SCE, and ability of cells to repair induced damage to DNA [7, 14, 15, 44, 45]. Except for the

TABLE 4

CHIASMA ANALYSIS IN 13 OF THE PROBAND'S CELLS AT DIAKINESIS THAT SHOWED NORMAL PAIRING

	No. bivalents/cell													
	Cell no.													
No. chiasmata/bivalent	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean bivalents/cell
0	1	...	...	1	1	...	...	...	...	1	1	...	1	0.6
1	2	7	4	6	4	7	4	4	2	5	2	3	4	4.9
2	15	10	13	8	13	13	13	11	15	11	16	15	14	12.9
3	5	5	6	8	5	3	6	5	4	6	2	5	4	4.1
4	...	1	...	...	...	...	...	3	2	...	2	...	...	0.5
Total chiasmata in cell	47	46	48	46	45	42	48	53	52	45	48	48	44	...
Mean chiasmata/cell														47.08

blood lymphocytes of one man [7], which exhibited a reduced ability to repair damage caused by uv- and X-irradiation, none was found to be abnormal. These negative results are not altogether surprising because neither asynapsis nor desynapsis seem to relate directly to recombination. In the repair- and recombination-defective mutants of *Drosophila* (*mei-9*, *mei-218*, and *mei-41*), development of SC and, presumably, synapsis are normal; however, the development of recombination nodules in them is abnormal, indicating that these mutations act on the mechanisms involved in recombination rather than on those involved in synapsis [46]. In contrast, in the asynaptic mutants of *Drosophila* [*c(3)G* and *mei-68*] and maize (*as*), recombination is abolished in unpaired chromosomal regions [4, 40]. Recombination is either unchanged or enhanced, compared with that in the wild type, in the paired chromosomal regions of asynaptic maize (*as*), and in desynaptic tomato (as_1, as_4, as_b) [36, 40]. Therefore, biochemical studies of mutations that affect meiotic pairing are likely to shed light on the molecular mechanisms of initiation and maintenance of synapsis rather than on those of recombination and repair.

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