An XYY Man with Progeny Indicating Familial Tendency to Non-disjunction

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THE XYY MALE has been conspicuously absent from the roster of human sex-chromosomal anomalies (table 1) that may arise as a result of meiotic and/or post-zygotic non-disjunction of the X and Y. There are three obvious reasons for the apparent scarcity of the XYY condition: Failure of meiotic YY separation is restricted to male gametogenesis, where it is further limited to the second meiotic division. Population surveys done for abnormal sex-chromatin in the buccal mucosa cannot differentiate between XYY and normal XY men. The male-determining function of the mammalian Y (White, 1960) and its relatively insignificant gene content, would minimize phenotypic disorders in a double-Y man. Such an individual should, therefore, not exhibit the pronounced anatomical, sexual and mental defects that facilitate the diagnosis of other abnormal karyotypes. Our case is the first XYY male on record (Sandberg *et al.*, 1961). Were it not for mongolism and other anomalies among his progeny he would have escaped the cytologist's curiosity. This underscores once more the advisability of extending chromosome study to relatives of patients with odd karyotypes.

OBSERVATIONS

Our subject is a 44 year old white man, 6 feet tall, without serious physical defects (Fig. 1a and 1b). He is of average intelligence and completed the second year of high school. He has earned his living through various manual tasks, but has experienced difficulty in keeping employers satisfied with his work performance. During his mid-20's he weighed about 195 pounds; now he tends toward obesity, fluctuating between 260 and 290 pounds. His past history includes brucellosis, a diaphragmatic hernia, and treatment for a peptic ulcer. The findings during a recent physical examination were unremarkable except for a diffusely scattered neurodermatitis, an umbilical hernia, and a cystic lesion of many years' duration in the left mandible. He is father of 7 living children from two marriages and professed continuation of adequate libido. His buccal mucosa is sex-chromatin negative, as in XY males.

The patient's chromosome constitution was determined on four occasions.

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TABLE 1. ABNORMAL SEX-CHROMOSOME PATTERNS IN MAN

Chromosome number	Pattern	Sex-chromatin	Phenotype	Reference*
45	XO	—	Turner's syndrome	(5)
45, 46	XO/XX	+	Chromatin + Turner's	(21)
45, 46, 47	XO/XX/XXX	+	Hermaphrodite	(4)
47	XXX	++	Double + female	(12)
48	XXXX	+++	Triple + female	(2)
47	XXY	+	Klinefelter's syndrome	(14)
46, 47	XX/XXY	+	Klinefelter's syndrome	(6)
48	XXYY	+	Klinefelter's syndrome	(18)
48	XXXY	++	Double + Klinefelter's	(3)
49	XXXXY	+++	Triple + Klinefelter's	(16)
45, 46	XO/XY	—	Hermaphrodite	(10)
45, 46	XO/XY	—	Amenorrhea	(1)
45, 47	XO/XYY	—	Amenorrhea	(13)
47	XYY	—	Male (present case)	(22)

*Reference is made only to the first cytologically well-documented case of each type.

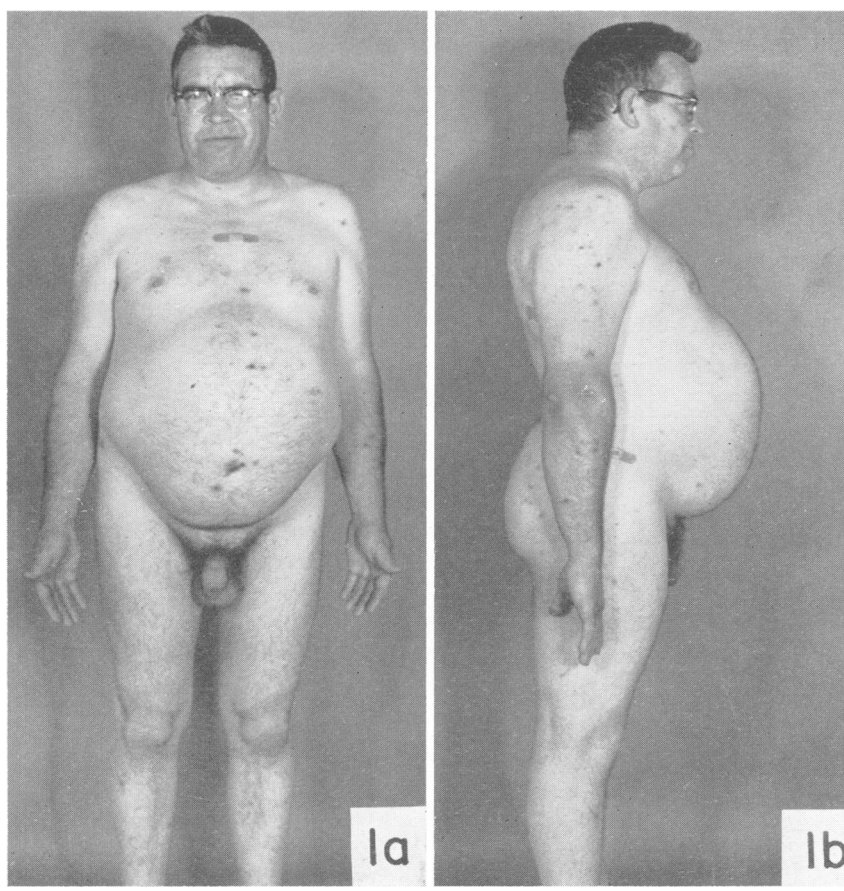

FIG. 1a AND 1b. Front and side view of XYY patient. The bandages on sternum and upper right hip cover punctures after marrow aspiration. (Feet, not shown in photograph, are normal.)

Two separate blood samples were cultured by the procedure of Moorhead *et al.* (1960). Freshly aspirated samples of sternal and iliac crest marrow were analyzed following the "direct squash" technique (Sandberg *et al.* 1960) Slide cultures grown from the skin were processed by an air-drying technique for flattening chromosomes (Rothfels and Siminovitch, 1958).

Table 2 summarizes the exact chromosome counts in blood, marrow and skin. Eighty-seven per cent of the 301 metaphases examined had 47 chromosomes (Figs. 2-5). Complete karyotype matching (as in Fig. 6) was performed on ten optimally spread metaphase plates. The presence of the small autosomal acrocentrics G21, G22 and the YY, was determined on 60 further metaphases, 58 of which contained 6 small acrocentrics. Arm-ratio and size of the small extra chromosome, identified in the patient's marrow, blood and skin, consistently matched the Y better than the autosomes G21 and G22. The Y is somewhat larger than the smallest autosomes, tends to be positively heteropyknotic, and has no satellites (Hauschka, 1961; Human Chromosome Study Group, 1960). Thus, the somatic constitution throughout the patient's body appears to be XYY.

TABLE 2. CHROMOSOME COUNTS IN THREE TISSUE SAMPLES OF AN XYY MAN

Tissue	Chromosome number					Total cells counted	Per cent of non-modal cells
	45	46	47	48	49		
Blood culture	1	9	168	6	0	184	8.7
Marrow*	1	8	68	0	0	77	11.9
Skin culture	1	4	27	7	1	40	32.2
Summary	3	21	263	13	1	301	12.6

*Counts made after "direct squash" technique without recourse to colchicine or tissue culture (21).

The incidence of non-modal cells, mostly with 46 and 48 chromosomes, was 8.7 per cent in the blood cultures and 11.9 per cent in freshly aspirated marrow—falling within the range of aneuploidy normally found in these tissues. The skin culture, however, exhibited 32.2 per cent of departures from the mode largely as a result of non-disjunction (about three times normal), and 15 per cent polyploidy arising by endoreduplication. Several clear examples of the latter, with typical 4-stranded chromosomes, were seen.

The patient's family history was elicited in as much detail as possible. His father is now 69 years old. His mother died in her 40's with carcinoma of the breast. His only siblings are two married sisters aged 43 and 36, both living and in good health. One sister is childless: the other has several normal children.

He has been married twice. The *first marriage,* to an apparently psychotic woman, terminated in divorce eight years ago. There were six pregnancies, as follows:

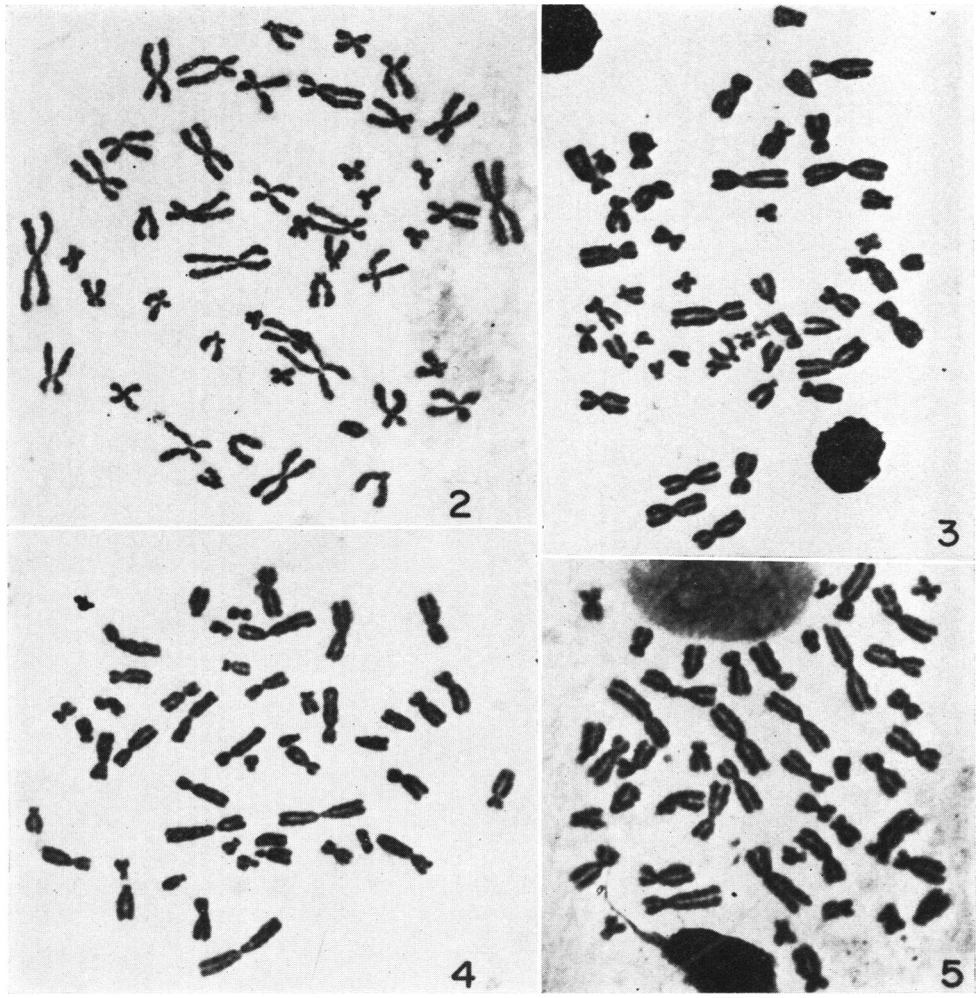

FIG. 2. Metaphase from cultured XYY blood. The two Y chromosomes lie near lower margin at about 5 and 7 o'clock.

FIG. 3. Metaphase from cultured XYY blood. The Y chromosomes appear on the margin of the plate at 3 o'clock, and three chromosomes inward on a radius drawn from 8 o'clock toward the center of the plate.

FIG. 4. Metaphase from cultured XYY blood. The two Y chromosomes may be seen somewhat inside 7 o'clock and to the upper right of center.

FIG. 5. Metaphase from cultured XYY blood. The two Y's are the second chromosome from the top, near 1 o'clock, and the third chromosome inward from 3 o'clock. (The metacentric on the upper left was pushed out of the field during squash preparation and was pasted in place.)

1. A now 18 year old daughter with amenorrhea who lacks breast development and was found to have no internal sex organs at laparotomy (for gallstones). The nuclei of her buccal mucosa were sex-chromatin positive. Chromosome determinations in her marrow and blood showed a normal female XX karyotype (81 counts of 46, 3 of 45, and 4 of 47). The possibility that she is

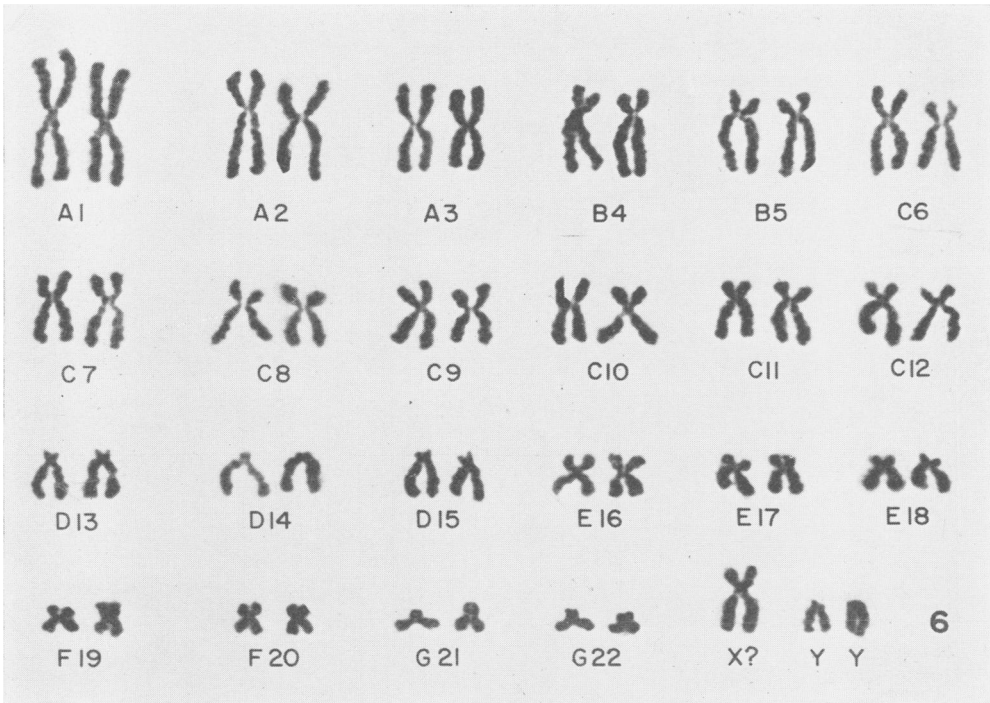

FIG. 6. Karyotype prepared from an enlargement of Fig. 2. One of the two Y chromosomes is positively heteropyknotic.

an XX/XO mosaic, i.e. a chromatin-positive case of Turner's syndrome, cannot be ruled out since only her blood-forming tissue and peripheral blood were examined.

2. The second pregnancy resulted in spontaneous abortion.

3, 4 and 5. These three apparently normal boys are now 17, 15 and 12 years old; they were anonymously adopted because of their mother's inability to care for them. We have so far been unable to obtain tissue samples for cytologic study.

6, 7. The last pregnancy of the first marriage resulted in the birth of fraternal twins, one of whom died after 3 days as a "blue baby." The other twin boy, now aged 10, has been adopted and is said to be in good health.

In the *second marriage* there were three pregnancies:

8. The first pregnancy terminated in a spontaneous abortion.

9. The second child is an outwardly normal, healthy 6 year old girl.

10. The third child is a 22 month old girl with mongolism. Thirty-two chromosome counts from a direct marrow squash obtained from this infant showed the characteristic trisomy in group G (27 metaphases had 47 chromosomes, 1 had 45, 2 had 46, and 1 had 48). Efforts are continuing to procure tissue samples from all the supposedly normal living progeny and from the patient's father.

DISCUSSION

The present XYY male fills the last blank space in the hypothetical list (table 3) of viable sex chromosome combinations produced by the union of normal and non-disjunctional gametes. Our subject is a fertile man not exhibiting any of the physiological, anatomical or mental defects that stigmatize XO, XXY, XXX and other individuals with unbalanced sex chromosome status. His asymptomatic masculinity (he is neither a deficient nor a "super" male) is instructive with regard to speculations about the male-determining potency and other gene content of the Y. Doubling of the Y produces apparently no drastic imbalance of the genome as a whole and is compatible with normal development.

TABLE 3. ZYGOTIC KARYOTYPES FROM ALL POSSIBLE UNIONS OF GAMETES WITH NORMAL AND ABNORMAL SEX-CHROMOSOME CONTENT

		♂ Normal		♂ Non-disjunction			
		X	Y	XY	O	XX	YY
♀ Normal	X	XX	XY	XXY	XO	XXX	XYY
♀ Non-disjunction	XX	XXX	XXY	XXXY	XXO	XXXX	XXYY
	O	OX	OY*	OXY	OO*	OXX	OYY*

*OO, OY and OYY zygotes are probably non-viable. All the viable somatic karyotypes in this table have now been encountered in the human population.

All the other patients so far described with unusual sex chromosome complexes involving both X and Y—XXY (Jacobs and Strong, 1959), XXXY (Ferguson-Smith *et al.*, 1960), XXXXY (Miller *et al.*, 1961), XXYY (Muldal and Ockey, 1960)—are mentally defective, and exhibit testicular dysgenesis together with some other features of Klinefelter's syndrome. The basic cytogenetic prerequisite for this phenotype appears to be a complement of two or more X chromosomes with at least one Y. It is interesting that Muldal and Ockey's XXYY Klinefelter's case had normal male body proportions except for pronounced gynecomastia, constituting perhaps an anatomical transition between the usual XXY phenotype and our masculine, fertile XYY case.

A somatic mosaic constitution of XO/XYY or XO/XY/XYY was recently reported by Jacobs *et al.* (1961) in a "woman" with amenorrhea. Her tissues were predominantly composed of XO cells, XYY being found in only 25 per cent of blood culture metaphases and 1 per cent of skin cells. There also was a low admixture of XY cells. The most probable mechanism for the origin of this mosaic would seem to have been post-zygotic nondisjunction of the Y chromosome during second cleavage in only one of the two first cleavage nuclei of a normal XY zygote. Despite the strongly male-determining character of the mammalian Y, maldistribution of the sex chromosomes during early cleavage may unsettle the developmental fate of a presumptive male zygote. A double dose of the Y chromosome was present in some body tissues of the "woman" with amenorrhea, yet male differentiation failed. The manifestation of sex in such mosaics probably depends on the proportion of XO:XY cells present in the

gonadal primordium. A case in point is the XY/XO hermaphrodite with ovotestis described by Hirschhorn *et al.* (1960).

Our XYY man is definitely not a somatic mosaic. His karyotype is best explained as resulting from fertilization of a normal ovum by a YY sperm (table 3). The only alternative diagnosis might have been trisomy for a group G autosome. This appears unlikely in view of the severe disorders regularly associated with autosomal trisomy. The only exception Fraccaro *et al.*, (1960) is a "normal" male with possible trisomy for chromosome F19, or tetrasomy resulting from centric fusion between two of the small acrocentrics in group G.

Identification of the extra chromosome in our XYY male was aided by the clearcut morphological criteria that set the Y apart from the two smallest autosome pairs, G21 and G22. The Y is somewhat longer than these two pairs of autosomes and has no satellites. Although calculations of arm-ratios for the tiny acrocentric Y involve rather subjective measurements, it seems agreed that the short arm of the Y is usually smaller than the short arms in group G, but variable in size. Observations of Y-chromosomal polymorphism in the human population can be explained both on genetic and morphologic grounds: According to Patau (1960), Y chromosomes with small deficiencies would have little selective disadvantage, and could therefore persist in the human karyotypic pool. Another source of fluctuating shape of the Y may be its high content of heterochromatin. This tends to retard its interphase replication rate relative to the autosomes, with consequent heteropyknosis and greater staining intensity. Makino and Sasaki (1961) consider the allocyclic behavior of the Y helpful in distinguishing it from the two smallest pairs of autosomes.

According to a recent estimate (Frota-Pessoa, 1961), the total rate of mutations to lethals and detrimentals acting at any time from early embryonic life to the early adult stage of man is 14-16 per cent. Our XYY propositus has 50 per cent defective progeny. His family history showing that 3/7 of the issue from the first marriage and 2/3 from the second marriage were phenotypically defective (1 amenorrhea, 1 blue baby, 1 mongolism, 2 miscarriages), and the explanation of his own XYY karyotype by non-disjunction of the Y in his father's gonad, indicate a hereditary tendency toward non-disjunction. A genetic trait affecting the mechanics of spindle function may be quite non-specific as to which chromosomes are maldistributed; it may operate during meiotic as well as during post-zygotic cell division. Faulty chromosome separation could have occurred in the zygote from which the patient's oldest daughter developed (sex-chromatin positive mosaic Turner's?), and is also suggested by the 3 times higher than normal frequency of non-disjunction (32.2 per cent) in cultures of his own skin.

Familial concentrations of abnormal karyotypes have been similarly interpreted by other observers. Miller *et al.* (1961) doubt whether the coincidence of an XXXXY male, two 21-trisomic females with mongolism, and a leukemic male in one family is a random event. Therman *et al.* (1961) emphasize the hereditary implications of the co-occurrence in one sibship of two conditions as rare as XO ovarian agenesis and the D-trisomy syndrome. They conclude that "a genetic control of meiosis could be taken for granted even if it had not been demonstrated in maize, Drosophila, and other organisms."

SUMMARY

A 44-year-old, asymptomatic, twice married, fertile white man of average intelligence was shown to have a somatic chromosome constitution of 47 in marrow, blood and skin. The extra chromosome has the morphologic characteristics of the Y. This individual is the first XYY male on record. His buccal mucosa is chromatin-negative. Four sons and a daughter are purportedly healthy. His abnormal progeny from both marriages includes a chromatin-positive daughter (46, XX) with amenorrhea lacking ovaries and uterus; a "blue baby" who died at 3 days of age; a mongoloid girl (47 chromosomes, typical G-trisomy), and two miscarriages. The 50 per cent incidence of defective offspring suggests possible familial predisposition to chromosomal non-disjunction.

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