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Males With an XYY Sex Chromosome Complement

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By early 1961 the combined use of the techniques of nuclear sexing and of the analysis of chromosomes from cultured marrow cells, lymphocytes, or fibroblasts had uncovered the existence of simple forms of sex chromosome aneuploidy in man characterized by an abnormal complement of X chromosomes. Knowledge was available on the 47,XXY male, the 45,X female, and the 47,XXX female. There was also information about sex chromosome mosaicism and about 46,XX females in whom one X chromosome was structurally abnormal, for example the 46,XXqi female. Furthermore, nuclear sexing had led in 1960 to the identification of the first example of a male with an abnormal number of Y chromosomes through the discovery of the 48,XXYY male. There was, however, no recorded example of the 47,XYY male, which was not suprising as his existence could not be detected by nuclear sexing and there was no way in which his likely phenotype could be surmised.

This deficiency was remedied in late 1961 when Sandberg and his colleagues published a preliminary announcement of the discovery of a male with an XYY sex chromosome complement, a discovery which might be labelled as a chance event, for the man in question was examined because he was the father of a mongol child and for no other reason. However, the word 'chance' should be used with some hesitation, for, as these investigators pointed out in their more detailed description of this man (Hauschka *et al.*, 1962), there may well be virtue in examining the relatives of those who are aneuploid.

Since 1961 the development of knowledge of the 47,XYY male has passed through two phases and is at present in its third phase. The discovery of the original case initiated the first phase, which was characterized by the description of a succession of cases apparently ascertained fortuitously from the examination of males with some physical abnormality, often in conjunction with a degree of mental retardation. In retrospect, however, as will be discussed, the description of these males as fortuitous ascertainments may be somewhat unjust. A suspiciously high proportion of them had undescended testes or delayed descent, and it is by no means certain that such findings may not be a feature of significant numbers of XYY males. At present there exist serious imperfections in our knowledge of the range of phenotypes that may be linked with this abnormal chromosome complement, and we cannot yet be certain that impaired testicular descent was merely a chance association with the XYY complement in some of the cases described in this first phase. By the end of 1965 some 12 examples of the 47,XYY male had been described as such in the literature, and, while other isolated examples have since been published, the first phase may be taken to have ended in 1965. The second phase was initiated in the same year when Jacobs and her colleagues published the preliminary findings from a formal chromosome survey of male patients in a maximum security hospital.

The feature of the second phase was the work of the British investigators on the males in maximum security hospitals. First, Jacobs *et al.* (1965) showed from their study of men in the State hospital at Carstairs in Scotland that there were numbers of men with a 47,XYY complement such as could not be reasonably attributed to chance. They also found that these men showed no consistent physical abnormality on a general clinical examination and, in particular, that in none was there evidence of impaired sexual development (Price *et al.*, 1966). A finding of no less importance was that the distribution of the heights of these males was quite significantly different from that of the heights of 46,XY males from the same hospital, the XYY males being on average about 15 cm. taller than the XY males. The second development was that Casey and his colleagues (1966b), examining the tall men at the English maximum security hospitals of Rampton, Moss Side, and Broadmoor, confirmed the findings

of Jacobs *et al.* that there must be unusual numbers of these men in the maximum security hospitals with a 47,XYY complement. Finally, Price and Whatmore (1967a, b), examining in detail the records and family backgrounds of the 47,XYY males from Carstairs, adduced evidence which strongly supported the idea that the behavioural disturbances of these men were primarily determined by their abnormal genotype.

This latter work marked the end of the second phase, and the third and current phase of study then developed, and one likely to last for a long time. In this phase the nature of the 47,XYY male is being investigated in depth and information is being gathered on his frequency in the liveborn population, in the ordinary population of adult males, and in a whole series of subgroups of the male population, ranging from prisoners to males in corrective training establishments, from boys in approved schools to those in schools for the educationally subnormal, and from men in hospitals for the mentally subnormal to those attending psychiatric out-patient clinics.

This review will approach the question of the nature and identity of the 47,XYY male in a historical perspective. It will deal in detail with the information gathered from the first and second phases of study, and it will discuss the present state of our knowledge in the third phase.

Definitions

It is necessary to adopt some definitions of the individuals to be discussed because of the known range of phenotype among those who are chromosome mosaics with a constitution of 45,X/47,XYY. Jacobs and her colleagues (1961) first described a phenotypic female with this form of mosaicism, who was 34 years old, only 147 cm. tall, and who had sexual infantilism. In other words she showed a number of the features of the 45,X female, and it may be relevant that her skin fibroblasts were almost entirely composed of 45,X cells and these cells constituted the dominant line in cultured lymphocytes. By contrast we have described a fertile and normally developed male with a 45,X/47,XYY complement, and in this man the XYY line dominated (Court Brown, Price, and Jacobs, 1968). Assuming that the sexual phenotype in these cases is in some way a function of the relative proportions of the two cell lines in the developing gonads during embryogenesis, then the range of phenotype from female to male may be explained on the basis that when the phenotype is female then 45,X cells wholly constituted or at least were predominant in the gonads during embryogenesis, and that the 47,XYY cells held sway in those showing a male phenotype.

There are, however, a number of reports of females with a 47,XYY complement (de Grouchy *et al.*, 1963; Vignetti, Capotorti, and Ferrante, 1964; Forsberg, Hall, and Ryden, 1965; Franks, Bunting, and Engel, 1967), three of which are difficult to explain on the argument that they are unrecognized mosaics of the 45,X/47,XYY type. The case of de Grouchy *et al.* may be relatively straightforward. The patient, a girl of 14 years, showed a number of features characteristic of females with a 45,X complement, particularly sexual infantilism, webbing of the neck, bilateral cubitus valgus, and retarded growth. The authors examined the chromosomes in cells from two blood cultures. There was evidence for a single cell line containing 47 chromosomes with the additional element being a small acrocentric chromosome. De Grouchy *et al.* were guarded in their conclusions, and while they considered the complement of this line to be most reasonably interpreted as 47,XYY they did not exclude the alternative interpretation of 47,XY,22+. However, in the light of experience, particularly of how in chromosome mosaicism the relative proportions of the constituent lines may vary widely from tissue to tissue, the most reasonable interpretation of the findings is that the chromosome complement of this patient is 45,X/47,XYY. It is possible that if the authors had examined tissues other than cultured lymphocytes, then they might have found a 45,X line. Even if they had not found direct evidence for such a line its presence in the gonads would have been a reasonable inference considering the phenotypic features of the patient. This particular case has also been reported by Bertrand *et al.* (1964).

The cases described by Vignetti *et al.* (1964), Forsberg *et al.* (1965), and Franks *et al.* (1967) have certain features in common, and all three differ from the case discussed above and reported by de Grouchy *et al.* (1963). Vignetti *et al.* reported on a 3-year-old female of normal growth and intelligence, who had a somewhat enlarged clitoris, a normally developed urethra but no vaginal orifice, and a mass in each labium majus eventually shown to be a testis. The uterus, Fallopian tubes, and ovaries were absent. Forsberg *et al.* (1965) reported on a 23-year-old woman with normally developed breasts and external genitalia but whose uterus and Fallopian tubes were absent. The right gonad was in the situation usually occupied by the right ovary while the left was in the region of the pouch of Douglas. Both were testes. The authors described this patient as a 46,XY/47,XYY/47,XXY

TABLE I

47,XYY MALES AND 48,XYY,21+ MALES NOT IDENTIFIED IN SURVEYS OR ON BASIS OF HEIGHT OR BEHAVIOURAL CHARACTERISTICS

Case No.	Age (yr.)	Ascertainment: Clinical Features	Reference
1	44	Mongol parent: normal IQ and sexual development	Sandberg *et al.* (1961) Hauschka *et al.* (1962)
2	2	Undescended testes and mental subnormality	Fraccaro *et al.* (1962)
3	8	Undescended testes and mental subnormality	" " "
4	12	Undescended left testis: normal IQ	Sandberg *et al.* (1963)
5	3	Sturge-Weber's syndrome	Dent *et al.* (1963)
6	11	Marfan's syndrome: normal IQ and sexual development	Hustinx and van Olphen (1963)
7	15	Mental subnormality: normal sexual development	Ricci and Malacarne (1964)
8	7	Hypospadias and hypogonadism	Milcu *et al.* (1964)
9	?	Identified family study: fertile	Stalder *et al.* (1964)
10	23	Hypogonadism: normal IQ	Court Brown *et al.* (1964)
11	3	Amyotonia congenita: undescended testes	Dunn *et al.* (1961); Uchida, Miller, and Soltan (1964)
12	9	Mongol: normal sexual development	Verresen and van den Berghe (1965)
13	18	Albright's disease of bone: normal sexual development	Montero and Duran (1965)
14	1	Mongol: normal sexual development	Migeon (personal communication, 1965)
15	14	Undescended testes, mentally subnormal	Kosenow and Pfeiffer (1966, 1967)
16	64	Hypogonadism	Balodimos *et al.* (1966)
17	26	?Hypogonadism	Nielson *et al.* (1966)
18	< 1	Mongol: undescended testes	Uchida, Ray, and Duncan (1966)
19	26	Idiopathic osteoarthropathy	Tzoneva-Maneva, Bosajieva, and Petrov (1966)
20	17	Retarded growth: normal testes, deficient hair	Mirouze *et al.* (1966)
21	39	Subfertility clinic: oligospermia, IQ 80–85	Wilton and Lever (1967)
22	52	Identified family study: fertile	Thompson, Melnyk, and Hecht (1967)
23	24	Neck webbing: mental subnormality, normal sexual development	Kelly *et al.* (1967)
24	8	Admitted psychiatric unit with destructive, defiant, antisocial behaviour; reported by Turner and Jennings (1961) as trisomy 22; since reassessed as 47,XYY; at 15 yr. 182 cm. tall; dislocation lens of right eye; bilateral retinal detachments with extreme myopia; IQ 50–55; assumed normal sexual development—see original report	Turner (personal communication, 1968)

mosaic, but a consideration of their reported count distributions suggests that these provide convincing evidence only for a 47,XYY line. These two cases reported by Vignetti *et al.* and Forsberg *et al.* had chromosome studies only on preparations of cultured lymphocytes, but the third case, reported by Franks *et al.* (1967), was most thoroughly studied and consequently is all the more valuable. The patient was a mentally retarded female of 21 months of age when first examined. Her growth was normal and she showed separate vaginal and urethral orifices. There was some slight enlargement of the clitoris, and a swelling was palpable in each labium majus as in the case of Vignetti *et al.*, while the uterus was impalpable on rectal examination. The child was re-examined at 38 months and the labial swellings excised. These are described as abnormal prepubertal testes. Extensive chromosome studies on lymphocytes, marrow cells, and fibroblasts from skin and from the right testis consistently showed a single line of cells with a 47, XYY complement.

These three cases have similarities enough to suggest that they represent a class of individuals with a female phenotype characterized by an XYY sex chromosome complement, absent internal genitalia, and gonads that are testes. Vignetti *et al.* did not put a name to the features of their patient, while Forsberg *et al.* described theirs as a case of testicular feminization. Franks *et al.* reported their case as an example of male pseudohermaphroditism. It seems difficult to substantiate a diagnosis of testicular feminization in the absence of a supporting family history. Furthermore, though we are ignorant of the true frequencies of individuals with 47, XYY complements and also of females with testicular feminization, it is stretching coincidence beyond the realms of reason to suggest that these three subjects represent the fortuitous association of testicular feminization and an XYY complement. The question does arise of just how these rare cases are to be regarded and whether they have a place among a possible variety of phenotypes linked with an XYY sex chromosome complement.

For the purpose of this review, however, the studies discussed will be limited to those of individuals with a male phenotype, and these include normally developed males, males with hypogonadism or hypogenitalism, and individuals with a 45,X/47,XYY complement who are phenotypically acceptable as males.

First Phase

The cases listed in Table I are isolated examples in which the karyotype was 47,XYY or 48,XYY, 21+, and none of which, to the best of one's knowledge, was identified from utilizing the information that became available from the work of Jacobs *et al.*

(1965), Casey *et al.* (1966a, b), Price *et al.* (1966), and Price and Whatmore (1967a, b), though perhaps the reassessment of Case 24, originally reported by Turner and Jennings in 1961 as 47,XY,22+, may have been influenced by the above work.

The original case, noted in a preliminary report by Sandberg *et al.* in 1961, was described in detail by Hauschka *et al.* in 1962. He was 44 years old, 183 cm. (6 feet) in height, and somewhat obese. Employed as a manual labourer it is noted that he had experienced difficulty in satisfying his employers. He was not mentally retarded but of low normal intelligence. This man was examined because his wife had given birth to a mongol daughter. In fact he had been married twice and had had 7 children. His sexual development was normal but he had a diffusely scattered neurodermatitis, an umbilical hernia, and a cystic lesion of unknown nature in the left half of his mandible.

The first marriage had ended in divorce, and there had been 6 pregnancies recorded with one ending in a spontaneous abortion. One daughter, with a 46,XX complement, has primary amenorrhoea due to the absence of internal genital organs. There are four apparently normal boys who have been adopted and who could not be examined. The youngest of these had had a dizygotic twin who had died in infancy from presumed congenital heart disease. The second wife had had 3 pregnancies, the first ending spontaneously in an abortion. The second child was a healthy girl, while the third was a mongol with a chromosome complement of 47,XX,21+. The authors conclude by noting that the 2 wives of the propositus had had 10 known conceptions between them, 2 ending as abortions and 3 resulting in abnormally developed children, and they suggest the possibility of an inherited tendency to non-disjunction involving at least two generations.

The remaining 23 cases listed in Table I have been ascertained for a variety of reasons. Two were found by chance during the examination of their families. In the instance of Case 9, the index case was a child with congenital abnormalities and with a chromosome complement of 46,XX, Cp+, an unbalanced form of the translocation present in her father expressed as 46,XY,t(Cp+;Dq−). This same balanced translocation was present in her grandfather whose chromosome complement was 47,XYY,t(Cp+;Dq−). Nothing more is known about the latter except, of course, that he was fertile. His wife had a normal karyotype and she had had 6 recorded pregnancies, of which 3 had ended in abortions and 3 in liveborn children. Two of the children were physically normal males with the balanced form of the translocation, while the remaining child, a girl, was dead at the time of study. There was reason to believe that she might have had an unbalanced form of the translocation. It is presumed that this poor reproductive record is related to the autosomal rearrangement and not to the XYY sex chromsome complement. The other chance ascertainment in a family study was Case 22. The index case was a boy with tyrosinuria, and in examining this boy's family his maternal grandfather was shown to have a 47,XYY complement. This had not impaired his reproductive ability for he had sired 6 males, all 46,XY, and one 46,XX girl. In view of the interest in the behavioural problems of 47,XYY males it is known that this particular man is somewhat hostile and has a history of brawling (Thompson, 1967, personal communication). These 2 cases in Table I (Cases 9 and 22), together with Case 1, already discussed, do indicate that at least some 47,XYY males are fertile.

No less than 9 of the remaining 21 cases were ascertained because of abnormal sexual development ranging from undescended testes to a degree of hypogonadism. The latter appears to be slight in Case 17, while Case 21 is simply described as having small testes. However, he was oligospermic with a sperm count of only 4×10^6 per ml., with 45% of the sperm being morphologically abnormal. Of the remaining 12 cases, 3 were ascertained as mongols and one of these had undescended testes; one was a case of amyotonia congenita and also had undescended testes, one had Marfan's syndrome but was sexually normal, 2 had mental retardation one being severe with Sturge-Weber's disease, 2 had bone disease, one retarded growth, and one webbing of the neck. The sexual development of all these latter cases was recorded as normal apart from Cases 5 and 19 for which there is no information. The last case of all, Case 24, was reported in 1961 as an example of trisomy 22, but this diagnosis is now considered incorrect with the more likely one being that of 47,XYY.

It is impossible, of course, to make any objective assessment from these cases as to whether the association in many of them between undescended testes or hypogonadism and the XYY sex chromosome complement was anything more than fortuitous. Subjectively, however, there is a suspicion that the association may be more than can be explained on the basis of chance. This suspicion is perhaps strengthened by considering how many males with undescended testes or with hypogonadism, and who did not have an abnormal nuclear sex, would require to be examined to find nine 47,XYY individuals, assuming the association to be

fortuitous. The key piece of information missing is that of the frequency of the 47,XYY male in the male population. If we assume, however, that he occurs with a frequency of 1 per 1000 liveborn males, then to find 9 such males from the examination of those with undescended testes or hypogonadism, who were chromatin-negative, would require chromosome studies on about 9000. It is doubtful if such numbers have been examined, and, therefore, there is a suspicion of a real association between the XYY sex chromsome complement and deficiencies of testicular development.

If the association is not explicable on the basis of chance then it is rather striking that so far, and to the best of one's knowledge, no 47,XYY male ascertained on grounds of aberrant behaviour has been found with defective testicular development. The final comment to make is that the possible association with either undescended testes or with hypogonadism, suggested by the data in Table I, is complicated by the fact that in one of the cases reported by Fraccaro *et al.* (1962, Case 2) the testes had descended by the time of publication of the report, while only one testis was involved in the case reported by Sandberg *et al.* (1963) and the patient had two 46,XY brothers in both of whom testicular descent had been somewhat delayed. A brother of the patient reported by Balodimos *et al.* (1966, Case 16) also showed hypogonadism while his sister, with a 46,XX complement, had had a late menarche and had stopped menstruating at 30 years.

Some comment is required on several of the other cases in Table I. Case 5 was originally reported by Hayward and Bower (1960) as an example of trisomy 22, but further studies by Dent, Edwards, and Delhanty (1963) clearly showed the additional acrocentric chromosome to be a Y chromosome. Case 6 was ascertained by chance during the examination of a family showing a number of members with Marfan's syndrome, while Case 7 was referred to hospital with pneumonia and examined cytologically because of his obvious mental retardation (IQ 59: Wechsler-Bellevue scale). More recent information (Ricci, 1968, personal communication) indicates that this last patient is very aggressive in his behaviour. The case reported by Court Brown *et al.* (1964) had also problems in social adjustment, and a more recent review of the information on him showed that not long before his study he had been convicted in Canada of breaking and entering and had been placed on probation. Case 13 showed features that were considered by Montero and Duran (1965) to be those of fibrous dysplasia of bone (Albright's syndrome), and in the same general context Case 19 is of interest as he showed the features of idiopathic familial hypertrophic osteoarthropathy. A finding of notable interest was that his father had the same condition and was a 46,XY/47,XYY mosaic (Table II). One is left wondering about a possible association between an XYY sex chromosome complement and bone disorders. Furthermore, Case 15 is reported to have mandibulo-facial dysostosis, and it should not be overlooked that the original case, reported by Sandberg *et al.* (1961) and Hauschka *et al.* (1962), had a lesion of undisclosed nature related to one side of his mandible. Finally, in a personal communication, 1968, Bosajieva has reported the finding of yet another male with idiopathic osteoarthropathy who has a 47,XYY complement.

Cases 20 and 23 could be chromosome mosaics. Case 20 was examined by Mirouze *et al.* (1966) because at 17 years of age he was only 143 cm. in height and 34 kg. in weight. His penis was small but his testes appeared to be normally developed. He had no growth of facial hair, no axillary hair, and only an early growth of pubic hair. Other features were radio-ulnar synostosis, some acetabular protrusion, and some irregularity of development of the vertebral bodies, and evidence for delayed epiphysial closure. Mirouze *et al.* reported his chromosome complement as 47,XYY or 47, XY,22+, but inspection of the photograph of the karyotype suggests the former to be the more likely complement. His short stature could be explained on the basis of his disordered bone development, but a combination of short stature, deficient body and facial hair, and delayed epiphysial closure suggests that a 45,X line may be present and that he may be a 45,X/47,XYY mosaic. Case 23 was reported by Kelly, Almy, and Barnard in 1967: there is very little information about this 24-year-old man except that he is mentally subnormal, has a history of suspected arsonist activities, and that his sexual development is normal. He was examined because he had a webbed neck, and a study of cultured lymphocytes showed a 47,XYY complement. The authors considered the possibility of 45,X/47,XYY mosaicism, but rejected this on the grounds that such individuals have a female phenotype. However, as has been noted, this is not necessarily so, and it is possible that further studies of this man might reveal a 45,X line, or alternatively the presence of neck webbing may be fortuitous.

In summary, therefore, the first phase of study led to the publication of a number of examples of males with a 47,XYY complement, the most common reason for ascertainment being either

undescended testes or hypogonadism. It is possible that there may be some link between impaired testicular development and an XYY complement and there may also be some link with bone disease.

Second Phase

To understand the events that led to the identification of unusual numbers of 47,XYY males in the British maximum security hospitals, it is necessary to recapitulate some earlier work on males in hospitals for the mentally subnormal. This was based on nuclear sexing and, therefore, the identification of males with abnormal numbers of X chromosomes.

In 1958 Ferguson-Smith reported finding 3 chromatin-positive males among 283 examined in a hospital for the mentally subnormal. Since then a good deal of work has been done on the frequency of males with abnormal complements of X chromosomes among the mentally subnormal, work recently reviewed by Court Brown (1968). There are on record at least 15 surveys of hospitalized mentally subnormal males, involving over 13,000 patients and in which the survey technique has been nuclear sexing. The over-all frequency of males with an abnormal nuclear sex is about 9·4 per 1000, comprising about 7·6 per 1000 singly chromatin-positive males, about 1·6 per 1000 doubly chromatin-positive, with the remainder being trebly chromatin-positive. These frequencies represent significant increases over those recorded in the live-born male population, and there is no doubt that the presence of an additional X chromosome or chromosomes appreciably increases the risk of a male being mentally subnormal.

It is also evident that among the mentally subnormal the frequencies of males who are chromatin-positive differ considerably for different ranges of IQ. For example, there are four surveys in which the patients may be distinguished as having IQ's of <50 or of 50 or more (Barr and Carr, 1962; Barr *et al.*, 1959, 1960; Mosier, Scott, and Cotter, 1960; Breg *et al.*, 1963; Hambert, 1966). Twenty-one of 3288 males with IQ's of <50 had an abnormal nuclear sex or 6·4 per 1000, while 32 of 1822 with IQ's of 50 or more were abnormal, a frequency of 17·6 per 1000. Excluding that of Hambert these surveys provide even further information on frequency in relation to IQ. For IQ's of <20 the frequency of chromatin-positive males is about 2·2 per 1000, for IQ's from 20 to 49 it is about 9·0 per 1000, and for those of 50 or more the three surveys give a frequency of about 15·2 per 1000. Fairly complete data are available on the chromosome complements of the abnormal males, again excepting the study done by Hambert, and these show that no XXYY male was found among those with an IQ of <50, but that such males constituted about one-third of the singly chromatin-positive males with IQ's of 50 or more.

The work of Hambert, referred to above, must be considered in a little more detail. Hambert widened and extended work originally reported in 1963 by Forssman and himself, and this report published the preliminary findings from nuclear sexing in a number of Swedish hospitals for hard-to-manage mentally subnormal males. There has been a tendency to regard it as relating specifically to penal institutions, and to conclude that because about 20 per 1000 males were chromatin-positive, in contrast to about 10 per 1000 in hospitals for the mentally subnormal, the difference represented a real distinction between criminals and mentally subnormal patients. But the conclusion that the Swedish hard-to-manage males constituted a group primarily defined by criminal activity was wrong. In Sweden every effort is made to deal with the mentally subnormal within the confines of the ordinary population. However, if an individual shows such gross and aberrant behaviour as to make this impossible then he is relegated to a hospital for the mentally subnormal, and it was such hospitals that Forssman and Hambert studied. For this reason it was perfectly legitimate to include the Swedish studies together with the results of other surveys of hospitals for the mentally subnormal. It would not be legitimate, however, to group these surveys with those of maximum security hospitals because the latter on the whole specifically deal with dangerous and aggressive, sometimes psychotic, and often mentally subnormal criminals.

It so happens that the frequencies of males with abnormal nuclear sex found by the Swedish workers are in close agreement with those found in the hospitals for the mentally subnormal in other countries after standardization for IQ. In fact, it seems reasonable to conclude that behaviour will be an important consideration in many instances in determining whether a mentally subnormal individual is hospitalized, certainly for those in the higher grades of subnormality. It is of interest in this regard that Court Brown reported in 1962 the finding that a high proportion of chromatin-positive males found in Scottish hospitals for the mentally subnormal had been referred to these hospitals via the Courts.

The work of Forssman and Hambert was followed by a nuclear sexing survey of the patients at two of the English maximum security hospitals by Casey *et al.* (1966b). There were Moss Side and Rampton which deal with mentally subnormal,

dangerous, and aggressive criminals. Nearly all the patients have an IQ of 50 or more, and about 25% an IQ of over 85 (Casey, 1966, personal communication). On the whole there is probably not too much difference in the distributions of IQ between the patients with IQ's of 50 or more in Moss Side and Rampton, the Swedish hospitals for the hard-to-manage, and the mental subnormality hospitals elsewhere. Casey *et al.* found 21 of 942 men to be chromatin-positive (22 per 1000); 7 of these men had a 48,XXYY complement, 12 a 47,XXY complement, while 2 were mosaics of the type 46,XY/47,XXY. The over-all frequency of chromatin-positive males found by Casey *et al.* is in close agreement with the findings from Sweden, and though these frequencies are somewhat higher than those from the surveys of the mentally subnormal by Barr *et al.*, Mosier *et al.*, and Breg *et al.*, as noted above, they are not significantly so. In fact, it would not be unreasonable to conclude that the frequency of chromatin-positive males in the maximum security hospitals of Moss Side and Rampton was not too different from that probably to be found among any institutionalized defectives with an IQ of 50 or more.

The results from Moss Side and Rampton were not published until 1966, but they were communicated to Dr. Patricia Jacobs in early 1965. At that time she was struck by the fact that 7 of the chromatin-positive males had a 48,XXYY complement. This contrasted sharply with the findings from a large study of patients in hospitals for the mentally subnormal in Scotland and from parts of England (Maclean *et al.*, 1962; Maclean, unpublished data). In this study only one of 30 men with an abnormal nuclear sex had an XXYY sex chromosome complement. All this gave credence to the idea that the additional Y chromosome in the 48,XXYY male might be adversely influencing his behaviour, and if this was so then 47,XYY males might be unusually frequent among men in maximum security hospitals. Later examination of the literature, however, brought to light the fact, already noted, that 3 of 10 singly chromatin-positive males identified in the surveys of Barr *et al.*, Mosier *et al.*, and Breg *et al.* of males with an IQ of 50 or more had a 48, XXYY complement. In other words the proportion of singly chromatin-positive males with this complement in these surveys of ordinary hospitals for the mentally subnormal was about the same as found in Moss Side and Rampton, and this suggested that the Edinburgh experience of hospitals for the mentally subnormal could have been unusual. In retrospect, therefore, it may be that the reason for suggesting that 47,XYY males might be unusually frequent in maximum security hospitals was wrong. However, whether right or wrong the postulate led to a chromosome survey of men in maximum security hospitals, and this ushered in the second phase of the build-up of knowledge about the XYY male.

The maximum security hospital at which Jacobs and her colleagues did a chromosome survey of the male patients was the Scottish State hospital at Carstairs in Lanarkshire. This is an institution provided by the Secretary of State for Scotland in terms of Part VII of the Mental Health (Scotland) Act 1960 for persons subject to detention under the Act, who require treatment in conditions of special security because of dangerous, violent, or criminal propensities. The hospital has one wing for the mentally subnormal and another for those with mental illness. At the time of the survey there were 342 male patients, 203 in the wing for the subnormal and 139 in the wing for the mentally diseased. Two hundred and forty-nine patients had been admitted directly via the Courts while 93 had been transferred from other places. All but 10 of the patients had a criminal record. The majority were classified as having a severe personality disorder of undetermined cause, while in a minority there was some physical explanation for their behaviour such as traumatic or infective brain damage or epilepsy or psychosis.

It was possible to study 315 of the 342 men, and 196 of those examined came from the wing for the mentally subnormal. The results of the examination of these 196 men formed the preliminary report by Jacobs *et al.* (1965) while the complete results are reported by Jacobs *et al.* (1968), and this latter report included information on all forms of abnormal chromosome complement found as well as the 47,XYY males. The report of 1965 showed that 12 of 196 men had an abnormal complement (6·1%) and that these included 7 men with an XYY sex chromosome complement (3·6%). In addition, there was a 48,XXYY male, a 47,XXY male, and a 46,XY/47,XXY/48,XXXY mosaic. The remaining abnormal men had autosomal structural aberrations. Though at this time there was no information at all on the frequency of the 47,XYY male at birth, all experience indicated that it was safe to assume that the finding of 7 of 196 males with such an abnormality was much greater than could possibly be expected on the basis of chance. The mean height of the men with a single Y chromosome was 170 cm. (67 in.), while the mean height of the XYY males was 186 cm. (73·1 in.). In fact nearly half the males of 183 cm. (72 in.) or more in this particular sample of men had two Y

chromosomes, a finding that clearly supported the contention that the relatively high frequency of 47, XYY males was not a chance finding.

When the survey was completed (Jacobs *et al.*, 1968) another 2 XYY males had been identified in the 119 men from the wing containing those with mental disease (1·7%), and the total tally of abnormal males among the 342 was 16 or 4·7%, including nine 47,XYY, one 47,XXY, one 46,XY/47,XXY/48,XXXY, one 48,XXYY, and four with autosomal structural aberrations. The mean height of the 9 XYY men was 181·2 cm., and between 1 in 3 and 1 in 4 of the men of 183 cm. or more had an XYY sex chromosome complement. Price *et al.* (1966) then examined the physical development of the XYY males, comparing them with others from the hospital matched as closely as possible for age, intelligence, and stature, the comparison being made with the examiners unaware of which men were the controls. There were no features which distinguished the XYY males from the controls, and all the former, except for one who was not willing to be examined, appeared to be normally sexually developed.

Though there was nothing physically remarkable about the XYY males, a comparison of these with other controls in respect of their behaviour revealed several interesting differences and one in particular which is important in assessing whether these men are genetically predisposed to behavioural disorders (Price and Whatmore, 1967a, b). In this study the 9 males with an XYY complement were compared with 18 males with an XY complement selected at random from those in the hospital categorized as having severe personality disorder of unknown cause, a category also covering the XYY males. The comparisons made were in respect of age at first conviction, the numbers of convictions for offences against the person and for those against property, and the number of convictions among sibs.

Three of the XYY patients had been convicted for the first time before the age of 10, and the mean age at first conviction for all the 47,XYY males was 13·1 years in contrast with 18 years for the controls, this difference being significant at the 5% level. The 9 XYY males had a total of 89 convictions of which 81 were for offences against property. The mean number of convictions per man was 9·0 for offences against property and 0·9 for those against the person. The 18 controls had a total of 178 convictions of which 46 were against the person (a mean of 2·6 per man) and 132 against property (a mean of 7·7 per man). Certainly these data suggest a bias towards crimes against property for the XYY males, but the comparison is a crude one and it would have been desirable to have taken account of the elements of time and opportunity.

The most informative comparison, however, came from an examination of the sibs of the XYY males and of those of the controls in respect of the numbers of convictions recorded against them. While the differences shown for findings in relation to age at first conviction and of numbers of offences can be argued to be of marginal importance, there can be no doubt about the significance of the fact that only one of the 31 sibs of the XYY males had been convicted of a criminal offence, while 139 convictions had been recorded for the 63 sibs of the controls, these latter sibs coming from 7 families. The single conviction of a sib in the XYY group was for a minor theft by a male with a history of mental illness.

As far as was possible, and subject to all the errors of retrospective recollection, information was obtained, from parents and also from some sibs relating to the childhood behaviour of the XYY males. Confidence in such data must be tempered by caution, for it cannot be denied that a parent faced with the fact of a son detained in a maximum security hospital may tend to exaggerate problems of behaviour in his or her son's childhood. Nevertheless it is the case that for 7 of the 9 XYY males ascertained by Jacobs *et al.* (1968) there was a history of behavioural problems extending back into early childhood, and in 4 instances the individuals had been sent to approved schools. In 2 instances the affected male had been disowned by his family.

From all these studies of the XYY males identified at the Scottish State hospital the picture emerged of psychopathic individuals lacking in any ordinary capacity for feeling, apparently without much depth of emotion, who seemed incapable of making any rational plans for the future, and who on the whole posed behavioural problems from childhood. Contrary to the impression given by the title of the preliminary paper by Jacobs *et al.* (1965) aggression was not an important feature of these men, though it appears from experience of later cases that some XYY males may be extremely aggressive. The investigators were left with the strong impression that these individuals, drawn from all the social classes, stood out as the black sheep of their families and as the apparently inexplicably erring sons in otherwise reasonably well-adjusted families. This picture strongly favours the idea that the additional Y chromosome genetically predisposes the 47,XYY male to the development of a psychopathic personality and to

consequent aberrant behaviour and antisocial conduct.

The Carstairs study did not shed light on whether the additional Y chromosome affected intelligence. The men examined were drawn from a highly selected group of males and their features need not necessarily be generally applicable to the whole class of 47,XYY males. There is only one last point to make about the study of these men and it is that a group of psychologists examined them using a variety of tests to see if cognitive or clinical features were detectable which distinguished them from other men in the hospital (Hope, Philip, and Loughran, 1967). This study was inconclusive and served perhaps only to underline the inadequacies of many psychological test systems.

The finding by Jacobs and her colleagues of the unusual distribution of the heights of the males with a 47,XYY complement in comparison with those with a 46,XY complement showed stature to be a useful marker for the identification of the XYY males. It will be recalled that about 1 in 4 males at the Scottish State hospital with a height of 183 cm. or more had an XYY complement. Casey *et al.* (1966a) took advantage of this finding and examined 50 males of 183 cm. or more at the English special hospitals of Moss Side and Rampton. They also examined 50 males from the English special hospital at Broadmoor which primarily deals with dangerous and aggressive individuals with mental disease. Their findings were startling and amply confirmed those of Jacobs *et al.* No less than 12 of the 50 males from Rampton and Moss Side had a 47,XYY complement, and 4 of 50 from Broadmoor had a similar complement. Though the findings from the surveys at Moss Side and Rampton unrestricted for height have yet to be reported, the fact that the frequency of XYY males among those of 183 cm. or more was so comparable to that among men in the same range of stature at Carstairs, suggests that the over-all frequency of these males will also be comparable, namely about 3%.

The significance of the findings in these maximum security hospitals depended on the argument that it was impossible to believe that the frequency of 47,XYY males at birth could be in any way comparable. In fact, it can be argued that their frequency at birth would be likely to be less than that of 47,XXY males. The little that is known so far on the frequency in male babies will be dealt with later. Casey *et al.* (1966a), however, did examine 30 ordinary males of 183 cm. or more and also 30 mentally ill males in the same range of height finding none with an XYY complement. Finally Casey *et al.* (1966a) reported also on the examination of 24 men of 183 cm. or more in an English prison, sentenced for periods between 6 months and 5 years. They found 2 to have a 47,XYY complement, and it is with this finding that the third and current phase of the study of the XYY male was opened.

Third and Current Phase of Study

The first examination of a group of prisoners by Casey *et al.* (1966b) raised the question of whether the frequency of 47,XYY males might be unusually high among the inmates of our prisons. This finding has led other workers to examine penal groups, and we may say that at present work is proceeding along two broad and general lines. The first is the survey of the chromosomes of males in a number of defined groups such as the liveborn male population, prisoners, boys, and young adults detained in training establishments for delinquents, and of patients in hospitals for the mentally subnormal and for the mentally diseased. In some of these studies all the males have been examined irrespective of their heights, while in others the surveys have been restricted to those of above some particular height. The second development has been the examination of individual males suspected of having a 47,XYY complement on the basis of their behaviour and height. Ultimately the most satisfactory information must come from the identification of these males at birth and their continued surveillance during childhood and adolescence and on into adult life. Only in this way will a real appreciation be obtained of the risks attendant on an XYY complement. However, to do this will require the routine examination of the chromosomes of the newborn population on a scale so extensive that it cannot be contemplated at present. For the meantime the best has to be made of deducing as far as is possible the natural history of the 47,XYY male from studies of those groups of subjects in which our limited information leads us to surmise that he may be unusually common. This section of the review will deal with such work as has been reported.

The assessment of this work is rendered difficult by our lack of knowledge of the frequency of the 47,XYY male at birth. We would expect, of course, that the 47,XYY male will be found to be less frequent in the liveborn male population than the XXY male, for the very reason that the error in parental gametogenesis which may lead to the conception of the latter can occur either at the first or second meiotic division in the female or at the first meiotic division in the male. The error leading to the conception of the 47,XYY male must only occur at the second meiotic division in the male.

It seems reasonable, therefore, to anticipate a lower frequency at fertilization of 47,XYY zygotes than of 47,XXY zygotes. While we do not know about the frequency of the latter at fertilization, we have a reasonable estimate of their frequency at birth, though admittedly this is virtually limited to studies of Caucasian populations. Pooling all the available information from nuclear sexing surveys of the live-born, and taking account of those surveys in which chromosome studies are reported on the chromatin-positive males, we may estimate the frequency of 47,XXY males at birth as about 1·3 per 1000 live-born males (Court Brown, 1968).

In Edinburgh we have examined 841 consecutive male births from two hospitals as part of a continuing survey of the newborn. To these we can add 266 randomly selected male births studied at an earlier time (Court Brown, 1967), giving a total of 1107 live births. Among these we have identified a single 47,XYY male, a single 46,XX male, 2 males with a 47,XXY complement, 2 with a 47,XY,21+ complement, and a single example of autosomal structural heterozygosity. These data do not suggest that 47,XYY males are particularly frequent.

It is exceptional for an adult 47,XYY male to be found by chance during the study of apparently physically normal males. The original case of Sandberg *et al.* (1961) must be scored as such and also Cases 9 and 22 in Table I. Recently Court Brown *et al.* (1968) have described a socially well-adjusted fertile adult male with a 45,X/47,XYY constitution found by chance during the study of a number of males who had had intra-arterial Thorotrast for the investigation of intracranial haemorrhage. Court Brown *et al.* (1966) reported the results of a chromosome survey of 207 adult males randomly selected from the ordinary adult population without finding a 47,XYY male. Possibly also one might consider here the case of Wilton and Lever (1966) noted as Case 21 in Table I. This man was ascertained when he and his wife were examined at a subfertility clinic, his wife having had one spontaneous abortion and one grossly malformed child. It could be, however, that such males may be unusually frequent among those seeking advice on fertility, though such data as exist do not support this. For example Kjessler (1966) examined 135 males attending a Swedish subfertility clinic, none having a 47,XYY complement. In Edinburgh, using the technique of blood culture, M. E. McIlree (unpublished data) routinely studied 143 males attending a subfertility clinic, but otherwise unselected, and found none with a 47, XYY complement. In an earlier study she and her colleagues examined the mitotic and meiotic chromosomes from 50 males, all being chromatin-negative and all having a sperm count below 20×10^6 per ml. (McIlree *et al.*, 1966). Again no 47,XYY male was found.

There is an important caveat to make about these studies on adults. They are dependent on voluntary co-operation, and studies such as those on males attending subfertility clinics are being done on a rather selected group of men who have sufficient insight into their own problems and a sufficiency of intelligence and drive to seek advice on a topic which still tends to be shrouded in an atmosphere of secrecy by society. It is entirely possible that some and perhaps many males with a 47,XYY complement will not be prepared to volunteer their participation in a study or will not have the necessary insight to seek advice in regard to subfertility. It is impossible to allow for the effects of bias introduced by refusals, and as far as the XYY males are concerned it seems entirely likely, considering what we now know of their behaviour, that they may be unusually prone to non-participation.

TABLE II

HEIGHTS OF 47,XYY MALES OF 15 YEARS OR MORE IDENTIFIED IN CIRCUMSTANCES IN WHICH HEIGHT HAS NOT INFLUENCED UNDERTAKING OF CHROMOSOME STUDIES

Height (cm.)	Age (yr.)	Reference
196	39	Wilton and Lever (1967)
191	64	Balodimos *et al.* (1966)
188	34	Jacobs *et al.* (1968)
186	31	,, ,, ,,
186	28	,, ,, ,,
184	28	,, ,, ,,
183	17	,, ,, ,,
183	44	Sandberg *et al.* (1961)
182	26	Nielson *et al.* (1966)
182	52	Thompson *et al.* (1967)
182	18	Montero and Duran (1965)
181	31	Jacobs *et al.* (1968)
181	23	Court Brown *et al.* (1964)
181	38	,, ,, ,, ,,
177	39	Jacobs *et al.* (1968)
175	32	,, ,, ,,
171	22	,, ,, ,,
169	17	Court Brown *et al.* (1968)

Distribution of Height. Reference has already been made to the findings by Jacobs *et al.* concerning the distribution of the heights of the 47,XYY males found in a survey of the Scottish State hospital, who were found on average to be about 16 cm. taller than the 46,XY males in the same hospital. This finding was used by Casey *et al.* (1966a) to identify 12 of 50 males of 183 cm. or more at Moss Side and Rampton as 47,XYY males, and since then studies have been done or

are in progress in which the study population is selected by height, for example, males of 183 cm. or more. This must lead, of course, to the identification of only a proportion of the 47,XYY males, and it renders difficult the assessment of the significance of the findings.

The heights of 18 XYY males are listed in Table II, all over 15 years of age and none ascertained in circumstances in which a consideration of height has influenced the choice of an individual for study. The heights range from 169 cm. to 196 cm., the mean being about 182 cm., with a standard deviation of 6·5 cm. The men listed constitute a heterogeneous group and one must be circumspect about drawing too many conclusions from the data. For example, some are mentally subnormal which in itself may have affected their stature, some are hypogonadal and the case reported by Montero and Duran (Table I) had Albright's disease of bone. For the present these data are all that are available, and they suggest that about 50% of adult 47,XYY males will be 183 cm. tall or more. On these data, surveys restricted to men of this height or more run the risk of failing to identify half the XYY males that may be present, while if the height restriction is placed somewhat lower at 178 cm. (about 70 in.) then about a quarter may be missed. Finally, the whole question is further complicated, especially perhaps when examining prisoners, by the question of malnutrition in childhood and the effect this can have on the ultimate stature of an individual. The data in Table II are heavily weighted by observations from males born before 1940, and in Britain at least males born since then, other things being equal, are likely on average to grow to a greater height than those born before 1940 because of improvements in the general standard of nutrition in childhood.

Persson (1967) has reported on a male 192 cm. in height (Case 7, Table III), none of whose male sibs was within 10 cm. of his height, and the author advocated research to see whether all adult 47,XYY males stand apart from the rest of their family in terms of stature. The data in Table III show that while this may often be the case it is not always so. The information is limited but the Table lists the heights of eight 47,XYY males and those of such adult male sibs as have been measured. Each of the four XYY males above 182 cm. exceeded in height his measured male sib or sibs, and in fact the taller the propositus the greater is the difference between him and the tallest sib. There are four XYY males with heights below 182 cm. In one instance the propositus is as tall as the taller of his two male sibs, in two instances the propositus is shorter than the tallest sib, and in only one instance does the propositus exceed the height of a male sib. Obviously a lot of interest may be generated from this type of comparison when more information becomes available, but it does seem that an XYY male may not necessarily be unique in his sibship in terms of height. It may be that when males are chosen for study on account of great height and found to have a 47,XYY complement then they will be unique among their sibs. However, there is a remarkable report by Wiener *et al.* (1968) of a 47,XYY male who was 210 cm. in height but who had a sister said to be about 218 cm. tall.

TABLE III

HEIGHTS OF 47,XYY MALES AND THEIR ADULT MALE SIBS

Height of Propositus (cm.)	Known Heights, Adult Male Sibs (cm.)	Reference
192	180, 177, 176, 174	Persson (1967)
191	180	Balodimos *et al.* (1966)
188	175	Jacobs *et al.* (1968)
186	182, 173, 173, 162	,, ,, ,,
181	171	,, ,, ,,
177	177, 163	,, ,, ,,
175	183	,, ,, ,,
171	174, 167, 165, 160, 152	,, ,, ,,

The use of a height restriction in surveying adult males stems from the natural desire to identify 47, XYY males with the minimum of effort. It does mean, however, that it is difficult to assess the significance of the findings unless these are clearly unusual, and it is necessary to make some estimate of what proportion of the adult males in the ordinary population who are above some defined height may be expected to have a 47,XYY complement. As some surveys have been concerned with males of 183 cm. or more, it seems worth while hazarding a guess at what may be expected in the ordinary male population in this range making a number of assumptions.

These assumptions are, first, that the frequency of 47,XYY in the liveborn male population is about 1 per 1000. Secondly, that the mortality risks of 47,XYY males do not differ from those of 46,XY males, while, thirdly, it is assumed that about 10% of the liveborn male population will reach a stature of 183 cm. or more as adults. This last assumption is based on recent data on the distribution of height among 18-year-old English boys (Tanner, Whitehouse, and Takaishi, 1966), and while 10% may be an overestimate in terms of males born before the last war, it may be an underestimate for males born at the present. It must also be emphasized that strictly speaking this may be taken to refer to British males. Fourthly, it is assumed that the data

TABLE IV

NUMBER OF 47,XYY MALES IN DIFFERENT-SIZED SAMPLES OF MALES OF 183 CM. OR MORE WHICH WILL BE SIGNIFICANTLY GREATER THAN NUMBER EXPECTED AT 1% AND 0·1% LEVELS PROBABILITY

Sample Size	No. of 47,XYY Males Found	
	$p < 0·01$	$p < 0·001$
50	3	4
100	4	5
200	5	6
300	6	7
500	8	10
1000	12	14

Note—Assumed population frequency of 47,XYY males among those of 183 cm. or more—1/200 (see text for assumptions made in deriving this frequency).

in Table II provide a valid indication of the distribution by height of adult 47,XYY males and that about half will be 183 cm. or more. From all these assumptions it is estimated that about 0·5% of the adult male general population of 183 cm. or more will have a 47,XYY complement. Table IV provides an indication of the number of 47,XYY males that would be required to be found in the examination of 50, 100, 200 etc. of men of 183 cm. or more for the number to be significantly greater at the 1% and 0·1% levels than that expected by chance. It must be stressed that this Table cannot be more than an approximate guide, and that it is based on an estimate of the frequency at birth which later work may show to be invalid. It is difficult, however, to believe that the birth frequency is likely to be much in excess of 1 per 1000 and it could be appreciably lower.

Parental Age. Table V shows the data on parental age at birth that are available for 42 of the males with a 47,XYY complement, the mosaics being excluded. The mean maternal age is 28·6 years and mean paternal age 30·9 years. Neither the means nor difference between the means provide evidence for an effect of paternal age.

TABLE V

PARENTAL AGES AT BIRTHS OF 47,XYY MALES

Age of Propositus (yr.)	Maternal Age (yr.)	Paternal Age (yr.)	Ascertainment	Reference
2	39	40	Undescended testes	Case 2, Table I
8	43	47	" "	Case 3, "
12	21	22	" "	Case 4, "
11	36	37	Marfan's syndrome	Case 6, "
15	19	23	Mental subnormality	Case 7, "
7	21	25	Hypospadias	Case 8, "
24	19	27	Hypogonadism	Case 10, "
3	34	31	Amyotonia congenita	Case 11, "
14	27	24	Undescended testes	Case 15, "
64	35	34	Hypogonadism	Case 16, "
26	24	26	"	Case 17, "
32	38	35	Oregon State hospital	Thompson (1967, personal communication
32	24	34	" " "	" " "
25	21	21	" " "	" " "
33	19	20	" " "	" " "
42	20	21	Court referral	Persson (1967)
33	46	43	Prison	Wiener *et al.* (1968)
21	29	32	"	" " "
52	32	38	"	" " "
8	23	26	Psychiatric clinic	Cowie and Kahn (1968)
0	25	23	Baby survey	Unpublished data, Edinburgh
13	29	36	Psychiatric clinic	" " "
16	24	26	Mental subnormality hospital	" " "
45	36	37	" " "	" " "
53	27	33	" " "	" " "
25	26	31	" " "	" " "
22	32	35	" " "	" " "
?	21	22	" " "	" " "
52	40	38	" " "	" " "
48	28	34	" " "	" " "
38	28	30	Prison	" " "
17	30	30	Borstal	" " "
17	32	33	Young Offender's Institution	" " "
38	29	31	Epileptic colony	" " "
31	27	30	Maximum security hospital	" " "
32	32	35	" " "	Jacobs *et al.* (1968)
39	20	22	" " "	" " "
17	23	30	" " "	" " "
31	41	41	" " "	" " "
28	23	22	" " "	" " "
22	28	34	" " "	" " "
28	32	37	" " "	" " "

TABLE VI

CHROMOSOME MOSAICS WITH A MALE PHENOTYPE AND HAVING 47,XYY CELL LINE

Case No.	Age (yr.)	Chromosome Complement	Ascertainment and Clinical Features	Reference
1	53	46,XY/47,XYY	Idiopathic osteoarthropathy; fertile; father of Case 19—Table I	Tzoneva-Maneva *et al.* (1966)
2	62	46,XY/47,XYY	Survey of males ⩾183 cm., mental disease hospitals; alcoholic; admitted informally after breaches of peace; normal sexual development	Court Brown *et al.* (1968)
3	34	45,X/47,XYY	Survey of males for radiation damage after Thorotrast; intracranial haemorrhage as boy; socially well adjusted; fertile normal sexual development	,, ,, ,,
4	44	47,XYY/48,XYYY	Survey of males in Australian prison; psychopath; murderer; IQ 94; no other data	Wiener *et al.* (1968)

Fertility. The evidence so far is limited and it is possible to do no more than say that some 47,XYY males are fertile. For instance, the data in Table I are biased by the presence of a number of males ascertained either because of failure of the testes to descend or delay in their descent or because of hypogonadism. However, there is no doubt about the reproductive ability of Cases 1, 9, and 22, which between them are known to have sired 18 liveborn children, 13 males and 5 females. For Case 1 there are no data on the chromosome complements of his sons, but all the sons of Cases 9 and 22 have been examined and all 8 males had an XY sex chromosome complement. It is also worth noting that the male with a 45,X/47,XYY mosaic constitution reported by Court Brown *et al.* (1968) had had two sons, both of whom had an XY sex chromosome complement, so that so far there are data on 10 sons without evidence of secondary non-disjunction. However, Case 19 (Table I) is the son of Case 1 (Table VI), a 47,XY/47,XYY mosaic, and the possibility of secondary non-disjunction cannot be excluded. Though many apparently normally developed 47,XYY males are and have been ascertained from the examination of various penal groups, it is often the case that these persons are unmarried, or if they are married and claim paternity then it is difficult to obtain access to the families to substantiate this claim and to examine the children.

Mosaicism with a 47,XYY Cell Line. The problem of the different sexual phenotype that may be encountered in subjects who have a chromosome complement of 45,X/47,XYY has already been discussed. The 4 known mosaics with a male phenotype and containing a 47,XYY line are listed in Table VI. One, already referred to, was a 45,X/47,XYY mosaic, whose sexual development was normal, who was socially well-adjusted, and who was fertile (Case 3, Table VI). Case 1 (Table VI) was the father of Case 19 in Table I, both father and son having idiopathic osteoarthropathy. Unfortunately no other data are available on this interesting family. Case 2 (Table VI) was identified in a study of tall males in mental disease hospitals. He was interesting as he had survived for many years as a casual labourer and without

TABLE VII

47,XYY MALES NOT IDENTIFIED IN SURVEYS BUT ASCERTAINED BECAUSE OF BEHAVIOURAL FEATURES AND HEIGHT

Case No.	Age (yr.)	Clinical Features	Reference
1	47	Aggressive psychopath, mental disease hospital; IQ 70–80; normal sexual development; ht. 184 cm.	Richards and Stewart (1966)
2	23	Epileptic and hard to manage; IQ 83; ht. 195 cm.	Forssman (1967)
3	32	Oregon State Hospital; armed sexual assault; normal sexual development; IQ 134; ht. 198 cm.	Thompson (1967, personal communication)
4	32	Oregon State Hospital; behavioural problems from childhood; armed assault and murder; IQ 86; scoliosis; normal sexual development; ht. 183 cm.	,, ,, ,,
5	25	Oregon State Hospital; behavioural problems from childhood; convicted for homosexuality; normal sexual development; myopia; scoliosis; IQ 90; ht. 183 cm.	,, ,, ,,
6	33	Oregon State Hospital; larceny and passing of bad cheques; sexual development, chordee but otherwise normal; IQ 85; ht. 185 cm.	,, ,, ,,
7	42	Referred by Courts for psychiatric study; robbery with violence; right testis atrophic, probably after sterilization; IQ 70; ht. 192 cm.	Persson (1967)
8	13	Aggressive delinquent; referred psychiatric clinic at 11 years; no other data; ht. 202 cm.	Court Brown *et al.* (1968)
9	8	Aggressive antisocial behaviour and truancy; normal physical development; IQ 95; ht. 145 cm.	Cowie and Kahn (1968)
10	26	Nervousness, bed wetting, and poor school performance; rebellious adolescence; symptoms of depression at 22 years; aggressive phantasies; normal sexual development; embezzlement; IQ 118; ht. 198 cm.	Leff and Scott (1968)

TABLE VIII
POPULATION STUDIES WITH NO HEIGHT RESTRICTION

Study Population	No. Examined	No. 47,XYY	Reference
Randomly selected liveborn males (maternity hospital)	266	0	Court Brown (1967)
Consecutive live male births (continuing survey two Edinburgh hospitals)	919	1	Unpublished Edinburgh data
Randomly selected adult males (Edinburgh general practices)	207	0	Court Brown *et al.* (1966)
Males attending subfertility clinic	135	0	Kjessler (1966)
Males attending subfertility clinic	143	0	Unpublished Edinburgh data
Males attending subfertility clinic; sperm count $< 20 \times 10^6$ per ml.	50	0	McIlree *et al.* (1966)
New entrants, Scottish Borstals for one year	607	1	Unpublished Edinburgh data
Allocation centre, Saughton prison, Edinburgh (males sentenced to 1 year or more)	302	0	" " "
An epileptic colony	72	1	" " "
Grendon prison for recidivists, England	204	2	Bartlett (1968, personal communication)
Mental subnormality hospital, England	605	0	Unpublished Edinburgh data
Maximum security hospital, Scotland	315	9	Jacobs *et al.* (1965, 1968)

evidence of serious antisocial conduct. His committal at the age of 62 to a mental disease hospital followed two charges for breach of the peace while under the influence of alcohol. In Cases 1, 2, and 3 listed in Table VI the 47,XYY line was the dominant line in preparations from cultured lymphocytes. There is no information on the chromosome count distribution for Case 4.

Isolated Examples of 47,XYY Males Ascertained because of Height and Behavioural Characteristics but not during Surveys. An increasing number of 47,XYY males are now being found because their height and behavioural aberrations suggest the possibility of the presence of two Y chromosomes, and those so far published are listed in Table VII. The IQs range from high grade mental deficiency to above average as in Case 3, who had an IQ of 134. Case 8 is of interest as the original account contains a detailed description of the patient's behaviour in childhood. In fact, he was first referred for advice at 4 years at which time he was said to be 'unmanageable at home, destructive, mischievous, and defiant'. His mother described him as having two personalities—'one considerate and happy, the other disgruntled and unstable'. At school his behaviour at times showed extreme aggressiveness. His physical health was good and he had an IQ of 95 at 5 years. Case 10 (Table VII) is also of interest. The patient came from a 'united, stable, and non-criminal social class I family', and eventually he was convicted of a well-planned embezzlement. He matches the concept of the 47,XYY male often appearing as the black sheep in a family.

Population Studies. The first group of studies to examine are those in which there has been no height restriction in the selection of males for examination (Table VIII). These range from those of liveborn male children and randomly selected adult males from the ordinary population to those in the Scottish maximum security hospital, in a specialized prison for recidivists, and to males of all ages in one large mental subnormality hospital. Information on the study of the specialized prison for recidivists has recently been published (Bartlett *et al.*, 1968). The men in this particular prison are largely recidivists with severe personality disorders, who have voluntarily been transferred from other prisons and are of generally good intelligence (mean score on Raven's progressive matrices—38). They are, therefore, a rather selected group of recidivists, a factor to be considered in assessing the results of their study.

The points to make about the data in Table VIII are, first, that the information from the baby studies and from the small randomly selected group of adults from the general population is compatible with a quite low frequency of 47,XYY males at birth. It has already been suggested that provisionally a birth frequency of about 1 per 1000 may be assumed for purposes of comparison, but that this may represent an overestimate rather than an underestimate of the real frequency. The finding of a single example among 607 young males, 16 to 21 years, sentenced for Borstal training, certainly does not suggest that disposal to a Borstal for a period of time is a particularly common way of dealing with the 47,XYY male. In this regard only 2 of the 9 XYY males found at the Scottish maximum security hospital had previously been sentenced to Borstal training (Jacobs *et al.*, 1968). The failure to find a single male among those going through the allocation centre at Saughton Prison, Edinburgh, is not particularly surprising. All these men had been sentenced for at least a year in prison, and this may be an important negative selection factor. The work of Price and Whatmore (1967a, b) suggested a preponderance of petty crime among the 47,XYY males with criminal

TABLE IX
SURVEYS OF MALES SELECTED BY HEIGHT

Study Population	No. Examined	No. of 47,XYY	Reference
Maximum security hospital, Scotland (ht. ≥ 183 cm.)	21	5	Jacobs *et al.* (1968)
English maximum security hospitals (ht. ≥ 183 cm.), Moss Side and Rampton	50	12	Casey *et al.* (1966a)
Broadmoor	50	4	
Atascadero State Hospital, California (ht. ≥ 183 cm.)	120	4	Thompson (1967 personal communication)
Patuxent Institution, Maryland, delinquent defectives			Welch *et al.* (1967)
ht. ≥ 183 cm. WAIS < 75	10	0	
ht. ≥ 183 cm. aggressive	10	0	
ht. ≥ 188 cm.	22	1	
All Scottish prisons (ht. ≥ 183 cm.)	106	1	Unpublished Edinburgh data
Scottish Young Offender's Institution (ht. ≥ 183 cm.)	16	1	" " "
Scottish Detention Centre (ht. ≥ 183 cm.)	4	0	" " "
Ohio State penitentiary (ht. ≥ 185·5 cm.)	100	2	Goodman and Smith (1967) Goodman (personal communication)
Wandsworth prison, London (ht. ≥ 183 cm.)	34	2	Griffiths and Zaremba (1967)
Nottingham Prison, England (ht. ≥ 183 cm.)	24	2	Casey *et al.* (1966a)
Pentridge Prison, Victoria, Australia (ht. ≥ 175 cm.)	40	5*	Wiener *et al.* (1968) and Bartholomew (1968, personal communication)
English approved schools 12–19 years; ht. at or over 90th percentile for age	29	3	Hunter (1968)
Scottish mental subnormality hospitals (ht. ≥ 183 cm.)	39	3	Unpublished Edinburgh data
English mental subnormality hospital (A) (ht. ≥ 183 cm.)	21	5	" " "
English mental subnormality hospital (B) (ht. ≥ 183 cm.)	19	2	Close, Goonetilleke, and Jacobs (1968)
Scottish mental disease hospitals (ht. ≥ 183 cm.)	112	1	Unpublished Edinburgh data
Mentally ill (ht. ≥ 183 cm.)	30	0	Casey *et al.* (1966a)
Normal males (ht. ≥ 183 cm.)	30	0	" " "
Industrial population (ht. ≥ 183 cm.)	371	0	Unpublished Edinburgh data

* Includes Case 4, Table VI.

records, and it is possibly unlikely that they will incur long prison sentences, especially if an important proportion of the 47,XYY males in this class are recognized as not only unstable in their behaviour but also mentally subnormal.

The other perhaps notable feature in Table VIII is that of the study of a single large English hospital for the mentally subnormal in which 605 males of all ages were examined, without one being found with a 47,XYY complement. This negative finding will be discussed later together with the findings recorded in Table IX, as there is evidence that 47,XYY males may only be found in substantial numbers in those hospitals for the mentally subnormal that specialize in behavioural problems and that draw a proportion of their patients from the Courts. In summary, it may be said that the only conclusively raised frequency of 47,XYY males is that recorded for the Scottish maximum security hospital, but that the finding of 2 of 204 in the Grendon prison for recidivists is likely to represent a significantly increased frequency.

There are a number of points to make about the data in Table IX. The studies referred to are those in which the selection of males for examination has been limited by their stature. Most of the studies are of men of 183 cm., but Welch, Borgaonkar, and Herr (1967), studied men of 188 cm. or more, Goodman and Smith (1967) men of 185·5 cm. or more, and Wiener *et al.* (1968) men of 175 cm. or more. The information in Table IV may be used as an approximate guide to the significance of the findings in those groups where men of 183 cm. or more have been examined, but it should be remembered that this information is based on several assumptions, notably a frequency of about 1 per 1000 for 47,XYY males at birth, and the use of the Table may lead to an underestimate rather than an overestimate of significance. Once again the findings in the British maximum security hospitals stand out as being very highly significant, and there is little doubt also about the significance of the findings in the Atascadero State hospital in California.

Table IX records a group of 7 studies from prisons and other penal institutions with a considerable divergence of results, ranging from 1 of 106 males of 183 cm. or more drawn from all the Scottish prisons over a limited period of time, to 5 of 40 males of 175 cm. or more from an Australian prison. These differences point to the likely operation of different selection factors determining the type of man in different prisons and probably also to different factors influencing the choice of men for study. The Scottish study attempted to overcome this by examining the men in all the Scottish prisons within a limited time period and the 106 men studied formed 95·5% of the men of 183 cm. or more in the prisons at the time of the survey. The remainder were either unavailable when the

prison was visited or were unwilling to provide a blood sample. The problem of the possible bias introduced by refusals has already been noted. The result of this study was disappointing, and the single 47,XYY male may well be a chance finding. It is difficult to know how to assess the findings of Goodman and Smith (1967). First, the lowest height was 185·5 cm. (73 in.), and, secondly, Goodman (1967 personal communication) indicates that a number of selection factors were involved. For instance, the men under sentence of death were not examined, nor were the men who were particularly violent and aggressive, while those volunteering were those with a greater degree of freedom based on a record of good conduct. It is possible that the finding of 2 in 200 with a 47,XYY complement may be not significantly above chance, but a final verdict must await more detailed information on the frequency in the ordinary population.

The findings in the small numbers of men examined at Nottingham prison and at Wandsworth prison suggest an importantly increased frequency. Unfortunately we know very little about these studies save that the Nottingham prisoners were those sentenced for periods ranging from six months to five years. However, if the frequencies found in these two English prisons were to be found in other English prisons, then this might suggest a difference between Scotland and England in the disposal of 47,XYY males. However, much more data are required to investigate this possibility. The findings in Pentridge prison in Australia are reminiscent of those in the maximum security hospitals with 5 of 40 men having a 47,XYY complement, including one man with a mosaic constitution—47,XYY/48,XXYY. The heights of the men were 178 cm. (2 men), 182 cm., 185·5 cm., and 210 cm.; 2 were murderers, one had committed murder, one had committed larceny, and the crime of the fifth is not recorded. Their IQs were 101, 94, 84, and 71 on the Weschler Adult scale, and the fifth is described as dull normal. Bartholomew (1968, personal communication) says that factors influencing the choice of men for study have been evidence for psychopathy (excluding the first 20 men he examined), and his own special research interests which account for the unusual number of murderers in the sample. It appears, therefore, that the findings in this study may be unrepresentative. All in all the prison studies do suggest that unusual numbers of 47, XYY males may be found in some prisons. It is likely, however, that there may be wide variations between prisons depending on the type or types of prisoner they accommodate.

The most recent report of all is that of Hunter (1968) who identified all of a group of 1021 boys at English approved schools with a height at or over the 90th percentile for their age. The range of age was from 12 to 19 years. Thirty-four boys were in this category of height of whom it was possible to examine only 29; 3 of the 29 had a 47,XYY complement.

A point of considerable interest relates to differences between the numbers and frequencies of 47, XYY males in different hospitals for the mentally subnormal. Table VIII shows that all 605 adult males have had chromosome studies done in an English hospital for the mentally subnormal without any example of a 47,XYY male being found. In striking contrast, Table IX shows for English mental subnormality hospital (A) the finding of five 47,XYY males out of 21 examined who were 183 cm. or more in height, and in the English hospital (B) the finding of 2 such males out of 19 examined, also of 183 cm. or more in height. Neither hospital may be regarded as a hospital designated to care for patients who show behavioural difficulties in the same way as are the maximum security hospitals, but both are hospitals for the mentally subnormal which make a feature of admitting patients from the Courts, this not being a practice followed by the English mental subnormality hospital noted in Table VIII. The data in Table IX, from a survey of males of 183 cm. or more in the Scottish hospitals for the mentally subnormal, are also relevant to the question of differences in admission policy and the frequency of 47,XYY males. So far 39 males have been examined, of which 3 have a 47,XYY complement. However, it is significant that 2 of the 3 abnormal males came from the same hospital, from the same ward in the hospital (a maximum security ward), and that they were the only 2 males in the ward of 183 cm. or more. Both had criminal records. The third 47,XYY male had, in fact, been transferred to his present hospital from the Scottish maximum security hospital where he was originally identified in the survey of Jacobs *et al.* (1965, 1968). It appears then that 47,XYY males are found in hospitals for the mentally subnormal, but that their distribution between these hospitals is not random.

The evidence so far from the Scottish study, together with the report by Casey *et al.* (1966a), is that 47,XYY males do not appear particularly frequent among males of 183 cm. or more who are in hospital for mental illness. Only two have been found to date in the Scottish survey, one of whom was a 46,XY/47,XYY mosaic (see Court Brown *et al.*, 1968), while Casey *et al.* found none in their

study. Neither of the Scottish cases had a criminal record though one, a man of 62 years, came to the notice of the authorities through drunken and disorderly behaviour.

Discussion

At present we are in the third phase of the development of our knowledge of the 47,XYY male. During the first phase a number of individual examples of these males was reported, and the discovery of two Y chromosomes followed the examination of individuals for a variety of reasons, commonly, however, because of some abnormality of the testes. Then the work of Jacobs and her colleagues (1965, 1968) and of Casey and his colleagues (1966a) led to the discovery of what could only be a quite significantly high number of these males in the British maximum security hospitals, and at the same time this work showed the unusual distribution of adult XYY males by height. All this has led into the third phase which is one of population surveys, mainly of maximum security hospitals or of prisons with often the men studied being restricted to those above some particular height which in most instances to date has been 183 cm. From all this information and effort it is hoped to put together some conspectus of the 47, XYY male.

It was noted earlier that males 'fortuitously' ascertained with a 47,XYY complement (Table I) contain a surprising number who were examined because of gonadal abnormalities, so much so that it may be the case that there is some real association between delayed testicular descent, or failure of the testes to descend, or hypogonadism and an XYY sex chromosome complement. Drawing a somewhat crude analogy with females having a 47,XXX complement, there could be a proportion of XYY males whose testicular development is defective in one way or another, just as there is a small proportion of XXX females whose ovarian development is not normal and who show secondary amenorrhoea. If this is so then it is surprising that no one has yet reported any abnormality of testicular development among XYY males ascertained because of aberrant and disordered behaviour. There are, of course, still comparatively few examples known of the XYY male, and it could be that with the identification of more of these males some will be found with defective testicular development whose ascertainment has depended on their antisocial conduct. It is tempting, however, to speculate that defective gonadal function may offset some of the risk of developing behavioural disorders linked with the presence of an additional Y chromosome. If this was so then account would have to be taken of the 48,XXYY male, for sufficient numbers of these hypogonadal males have been described in circumstances from which it is fair to conclude that such males have a heightened risk of exhibiting aberrant behaviour. For these men, however, it can be argued that the additional X chromosome may also be an influential factor in their abnormal conduct for there seems little doubt that XXY males as a class also show an unusual tendency towards aberrant behaviour.

It is fair to suggest from the above considerations that our knowledge of the range of phenotypes associated with a 47,XYY complement is possibly far from complete, and that in concentrating on males with gross antisocial conduct, as currently is being done, we may be guilty of biased selection. If, for example, an estimate of 1 per 1000 liveborn males having a 47,XYY complement is anywhere near the truth, and if such males are not subject to strong adverse selection during childhood through enhanced mortality risks for various diseases, then there is a large gap between the numbers that are present in the male population and the numbers being recognized in prisons, maximum security hospitals, mental subnormality hospitals, mental disease hospitals, and the like. For instance, the Scottish population of males of 15 years or more in age is about 1·8 million, so that given a frequency at birth of about 1 per 1000 there could be as many as 1800 47,XYY males in the adult male population. So far the studies carried out in Scotland have only identified about 2% of this number.

There are so many unknown factors that the sort of estimates that have been made in this review have to be regarded with considerable circumspection. In the end there can be no substitute for an extensive and prolonged study of newborn children. Very adequate grounds for justifying such studies come from considering what is known at present about the over-all frequency of children at birth with an abnormality detectable in mitotic cells. This appears to be about 10 per 1000, and there is much to be said for the eventual development of the routine screening of the newborn once automated facilities become available for the fast throughput of analysed cells. Many of the problems posed by the 47,XYY male can only be satisfactorily answered by their identification at birth and their surveillance from birth onwards. In this way it will become possible to assess what are the chances of any liveborn XYY male developing extreme behavioural aberrations, and, of course, if these risks are ultimately shown to be substantial then preventative measures through adequate training are only

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