Chromosome survey of total population of mentally subnormal in North-East of Scotland

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Summary. A cytogenetic survey of the complete population of mentally subnormal in the North-East of Scotland has been undertaken. A register for the mentally subnormal within the region already existed, and all persons recorded, whether they resided at home or in subnormality hospitals or other institutional care, were included. The total number recorded was 3020 and of these 2770 were examined cytologically. In all 297 (10.7%) were shown to have a chromosomal abnormality, and of these Down's syndrome accounted for 250 (9%). Within this category was an unexpected excess of males. Deletions and supernumeraries comprised the remaining autosomal anomalies. Increased numbers of sex chromosome abnormalities among high grade mentally subnormal individuals were confirmed for both sexes. The survey has shown that abnormal chromosome complements contribute significantly to the causation of mental retardation, and has also provided estimates which cannot be obtained from hospital surveys alone.

The North-East of Scotland is for several reasons an area particularly suitable for epidemiological studies. First, the population at the time of the survey (1966–71) was relatively static and any migration has been largely within the region. Secondly, the principal hospital facilities of the former North-Eastern Regional Hospital Board are centred in Aberdeen, where the University is also situated. The main disadvantage is that the population of 480 000 is scattered over a large area of the mainland and the northern isles of Orkney and Shetland.

The origin of the register for the mentally subnormal has already been described (Innes, Kidd, and Ross, 1968) and in the present paper we report on the results of a cytogenetic survey of these individuals. The survey formed part of a comprehensive study on biochemical, social, psychological, and family aspects of the registered individuals. These other results will be presented elsewhere.

All persons on the register were included, whether they resided at home or in subnormality hospitals or other institutional care. The availability of beds and the policy regarding admission should not, therefore, affect ascertainment. Some individuals in fact changed their placement during the course of the survey. However, facilities for the identification and care of the retarded, which are closely linked functions, have been developed at different rates in the various counties within the region. In the more remote areas also, there is little incentive to notify such individuals, especially when high grade. These people are often accepted in rural communities and gainfully employed. Such factors will lead to under-ascertainment, again, particularly for the high-grade individual who has left school and also for preschool children with mild defect who may not be recognized unless other malformations are present. In contrast, notification is likely to be most complete in the City of Aberdeen because of the early provision of facilities, culminating in the opening of a special school in 1956, and in the whole area, for those of school age. The final number of those included in the survey

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was 3020. Omissions are inevitable and will have resulted in some bias with respect to the cytogenetic data, since the majority of those not tested are living in the community and are presumed to be high grade. Refusals may have excluded preferentially some individuals with sex chromosome anomalies which would, therefore, be underestimated.

The cytogenetic studies represent a unique attempt to investigate a complete population of the mentally retarded, regardless of place of residence or type of institution. They provide an estimate of the contribution to mental retardation by chromosome anomalies, which cannot be obtained from hospital surveys.

Methods

In all cases chromosome preparations were made from short-term cultures of lymphocytes. Blood samples, 5 to 10 ml, were obtained and placed in sterile 10 ml tubes containing heparin. For young children, where only capillary blood could be obtained, tubes containing 2 ml tissue culture medium were used. The delay in arrival of samples at the laboratory was dependent on the area of collection but was sometimes as long as three days. After the initial culture had been made, the remainder of the sample was stored at 10 to 15° C, to allow repeat cultures to be set up if required. This was important in view of the geographical scatter of the individuals.

Whole blood, 0.4 ml, was added to 4.0 ml tissue culture medium (TC199), with 1.0 ml autologous serum and 0.1 ml phytohaemagglutinin (Wellcome). Duplicate cultures were set up, so that if the first, harvested after 72 hours at 37° C, failed, the second could be processed. Slides were made by standard procedures, and a minimum of 10 cells was counted. Initially, two cells in each case were photographed and karyotyped. Later it was considered adequate to analyse visually only two cells which were also photographed, but not karyotyped, and the negatives stored for future reference. Abnormal complements were still karyotyped, except for trisomy 21. In cases with more than one cell line at least 30 cells were scored. Cultures showing an abnormal pattern were repeated wherever possible, except for standard trisomy 21. Where appropriate, autoradiography, C-, G-, and Q-fluorescence banding techniques were used (Paris Conference, 1971).

For the sex chromosome abnormalities, where peripheral blood cultures had been used as the initial method of investigation, sex chromatin was examined when a second sample of blood was obtained. A modification of the buccal smear technique of Moore and Barr (1955) was used.

Results and discussion

Table I shows that of the 3020 individuals included in the survey, 1693 were males. Chromosome results were obtained in 1565 males (92.4%)

TABLE I
SUMMARY OF CYTOGENETIC FINDINGS

	Males	Females	Total
Total individuals on the register	1693	1327	3020*
Total individuals analysed	1565	1205	2770*
Trisomy (including partial) 21	153	97	250
Autosomal deletions	4	3	7
Supernumerary chromosomes	4	5	9
Sex chromosome anomalies	25	6	31
Total chromosomally abnormal (%)	186 (11.9)	111 (9.2)	297 (10.7)

* 91.7% of the population analysed.

and in 1205 out of 1327 females (90.8%), totalling 91.7%. The higher percentage of males with chromosome anomalies, 11.9% as compared with 9.2% of females, is accounted for partly by the expected excess of sex chromosome syndromes, but also by an excess of Down's syndrome. Supernumerary chromosomes were present in 9 individuals, and apparent deletions of autosomes in 7 others.

I: Autosomal abnormalities

A: Down's syndrome. As expected, this was by far the most frequent clinical diagnosis, being confirmed cytologically in 250 of 267 individuals. From 17 no sample was obtained or the cultures were unsuccessful, 7 having died during the course of the survey. D/G or G/G translocations were present in 5 of the 250 individuals (2.0%) and standard trisomy G in the remainder. Ten of the latter (see Table II) showed mosaicism with a normal cell line (4.0%).

One patient was found to have 47 chromosomes, the additional G group chromosome being shown by fluorescence to be a 21, but she had not been diagnosed as Down's syndrome. Reassessment of the clinical features of this patient did indeed suggest that she had Down's syndrome. No survey data were obtained on one patient who had been seen

TABLE II
DOWN'S SYNDROME

Chromosome Constitution	Males	Females	Total
47,21 +	144	91	235
46/47,21 +	7	3	10
46,D/G	2	1	3
46,G/G	0	2	2
Not tested	8	9	17
	161	106	267

TABLE III

AGE DISTRIBUTION AND SEX OF PATIENTS WITH TRISOMY 21

Date of Birth	No. of Males	No. of Females	Total	Sex Ratio	Sex Ratio of General Population*
1960-1969	22	18	40	1.222	1.054
1950-1959	37	23	60	1.609	1.051
1940-1949	45	23	68	1.956	1.037
1930-1939	25	19	44	1.316	0.986
1920-1929	13	6	19	2.166	0.956
1910-1919	7	5	12	1.400	0.863
Total	149†	94	243	1.585	0.998

* Data taken from Registrar General of Scotland Annual Report, 1973.

† Two males born before 1910.

during an admission to hospital when the diagnosis of Down's syndrome was confirmed clinically and cytogenetically.

A diagnosis of Down's syndrome was noted for 8.9% of those patients on the register, and in 9.8% of those in the subnormality hospitals. These figures compare with the 10% quoted by Penrose (1938) and 8.3% by Newton *et al* (1972a) for those in the retardation hospitals. Of interest is the preponderance of male Down's syndrome cases (Table III). In the whole series there were 161 male Down's syndrome cases, in 151 of whom trisomy 21 had been shown, compared with 94 out of 106 female Down's syndrome cases (Table II). An approximately equal sex incidence would be expected at birth (with a slight excess of males, sex ratio approximately 1.05). However, in our series, there is an excess of males, which is particularly striking from the second decade onwards. Placement should not have produced this bias since all individuals known to have Down's syndrome have been included. However, it should be noted that a higher proportion of males than females (57/94 v. 25/68) were in subnormality hospitals or other residential accommodation. Preferential admission of males with Down's syndrome may, therefore, have overemphasized the proportion of males in some of the series reported in Table IV. A greater mortality among females with Down's syndrome was noted as long ago as 1932 by Penrose, though little attention was paid to this observation. In our series, of the 20 Down's patients who have died since the initial survey in 1966, 12 were females, a proportion in line with the general trend. Recent data of other workers are summarized in Table IV and appear to indicate an excess of males. In the largest series of Fabia and Drolette (1970) and in that of Collmann and Stoller (1963), both of whom attempted complete ascertainment, the sex ratio is unaltered. It should be

TABLE IV

SEX RATIO IN DOWN'S SYNDROME

Authors	Males	Females	Total	Ratio
Record and Smith (1955)	139	113	252	1.23
Carter (1958)	398	300	698	1.33
Collmann and Stoller (1963)	370	359	729	1.03
Forssman and Åkesson (1965)	681	582	1263	1.17
Engel <i>et al</i> (1970)	156	140	296	1.11
Fabia and Drolette (1970)	1241	1180	2421	1.05
Dey (1971)	270	230	500	1.17
Newton <i>et al</i> (1972a)	62	42	104	1.48
Sutherland and Weiner (1972)	166	105	271	1.58
Gardner <i>et al</i> (1973)	530	442	972	1.20
Lindsjö (1974)	242	196	438	1.23
Present series	151	94	245	1.60

noted that Fabia and Drolette sought to identify only those born between 1950 and 1966, so that a differential mortality in the older age range would not have been detected. This reservation does not apply to the series of Collmann and Stoller. On the other hand, a high sex ratio is found in the three other area surveys, those by Gardner *et al* (1973), Lindsjö (1974), and Record and Smith (1955). Preferential admission of males to hospital, which we have shown to occur, cannot be the explanation for the high sex ratio either in these two or in our series. What is known, is that there is an excess mortality among females, particularly in early childhood which may be the result of congenital heart disease (Carter, 1958; Record and Smith, 1955; Collmann and Stoller, 1963; Fabia and Drolette, 1970). Whether there is a similar differential viability *in utero* is yet to be determined.

One interesting cluster of 8 patients, including 2 pairs of sibs, occurred on the Island of Yell, the second most northerly of the Shetland Isles with a population of 1150. These had already been identified clinically by Ross, Innes, and Kidd (1967). The incidence of 6.94 per 1000 individuals is nearly seven times greater than the rate in the newborn on the Scottish mainland (~1.0 per 1000 (Jacobs *et al*, 1974)). We suspected inheritance of the translocation type of Down's syndrome. On chromosomal analysis, however, only the standard trisomy has been found, but there was a significant increase in the maternal age of the 6 mothers.

Over the whole series an increased average parental age is evident. The mean maternal and paternal ages are, respectively, 35.3 and 37.9 years, excluding those patients with mosaicism. The corresponding figures for mosaic patients are 34.4 and 36.2 years. They compare with figures of 28.1 and 32.1 for the

respective maternal and paternal ages of all individuals on the survey with a normal chromosome pattern.

Translocations. Of the 5 patients with a translocation 3 were DqGq and 2 GqGq. The chromosome patterns of both parents of 4 were all normal so that these were new mutations. Only the mother and sister of the fifth with a DqGq translocation were available for study. The chromosomes of both were normal despite the mother's poor obstetric history. Out of 10 pregnancies only 2 reached term, 7 ending in spontaneous abortion at 3 to 4 months' gestation. The father may be a balanced carrier of a DqGq translocation, but he was not available for study. The mothers of these 5 patients were aged between 25 and 29 (average 26.2 years) at the birth of their affected child and the fathers between 25 and 36 (average 29.8 years). The average age is, therefore, lower than that of parents whose children have standard trisomy 21 and corresponds with previous findings.

Our finding of only 2.0% of translocations is lower than in most larger series. Where there has been selection for young maternal age it may be as high as 9% (Mikkelsen, 1971). The figure from the largest series reported by Matsunaga and Tonomura (1972) was 5.1%. On the other hand, Engel *et al* (1970) gives 2.6% for his personal series and 2.9% for combined series, while Mikkelsen (1971) quotes an over-all value of 3.2%. Variation in the larger series is difficult to explain unless an excess of younger mothers and their affected children has inadvertently been included because of a bias towards referral of this group by their own physician. This is suggested by comparing specially referred patients and those apparently unselected. Engel *et al* (1970) found no Robertsonian translocations among 170 Down's syndrome cases from institutions for the mentally retarded and 7 out of 142 (4.9%) where there was some degree of selection. Similarly, Sergovich, Soltan, and Carr (1965) contrasts 2.1% with 6.2% among selected Down's syndrome cases. Taking only the larger series from populations of European origin where there is no apparent selection, the frequency is 3.1% including the present series and 3.2% without it (Table V). Translocation, therefore, may be a less frequent finding in Down's syndrome than was previously thought.

Mosaicism. Ten individuals showed mosaicism of the 46/47 + 21 type. The percentage of trisomic cells varied considerably, two or more blood cultures being studied in all but one case. The samples were widely separated in time and the initial culture

TABLE V
UNSELECTED SERIES OF DOWN'S SYNDROME

	No. Reported	D/G	G/G	Mosaic + G
Sergovich <i>et al</i> (1964)	96	0	2	N.K.
Chitham and MacIver (1965)	105	3	1	3
Richards <i>et al</i> (1965)	224	2	3	6
Engel <i>et al</i> (1970)	170	0	0	2
Moser and Wolf (1971)	244	2	4	6
Hongell, Gripenberg, and Iivanainen (1972)	174	3	5	1
Newton <i>et al</i> (1972a)	104	4	1	4
Lindsjö (1974)	365	10	8	11
Present series	250	3	2	10
	1732	27	26	43 (2.5%)
		53 (3.1%)		

had always shown two cell lines. Such variation has been shown previously by Taysi, Kohn, and Mellman (1970), 4 of their 7 patients showing statistically different percentages at different sampling times.

All our mosaic patients showed sufficient evidence of Down's syndrome for the diagnosis to be made on clinical grounds alone. In one individual 8% of cells contained an extra small acrocentric chromosome, probably a G group autosome rather than a Y, but a further culture showed only 46,XY cells. With knowledge of the cytogenetic studies, features of Down's syndrome were observed, though insufficient for this diagnosis to be sustained. It is unlikely that a diagnosis of trisomy 21 mosaicism would have been made in other individuals with no definite features of Down's syndrome and where cells with trisomy 21 might have constituted a minor cell line (cf. the presence of a minor cell line with trisomy 21 in the mothers of some patients with Down's syndrome, e.g. Blank *et al*, 1962; Kaffe, Hsu, and Hirschhorn, 1974).

The figure of 4.0% for mosaics among the Down's patients in this survey is higher than those of 2.3% and 2.1% derived from combined series by Engel *et al* (1970) and Richards (1969), but similar to the figure of 3.8% of Newton *et al* (1972a). The figure, using the apparently unselected larger series, is 2.5% (Table V). One reason for the variation between the series may be methodological, for example, the number of cells examined initially.

B: Autosomal deletions. In this series three types of deletion occurred.

Cri du chat syndrome. Five individuals with a deleted short arm of a No. 5 chromosome were detected. The original identification was based on measurement, supplemented where possible by

autoradiographic, fluorescent, and ASG chromosome banding techniques.

Three cases were sporadic. One aged 11 had features typical of the syndrome and deletion of 30% of the short arm (Fig. 1a). The second was born in 1945 and has the features now recognized as those

found in adult patients (Breg *et al*, 1970). The third, born in 1944, is merely retarded without any physical pointer to the diagnosis. It may be significant that in this third patient the deletion is the smallest, approximately 20% (Fig. 1b) compared with 50% in the other adult (Fig. 1c). This is in contrast to the report of Miller, Warburton, and Miller (1969) that there is a consistency in the clinical findings despite variation in size of the deletion. These patients appear to have been detected clinically and with this mode of ascertainment an element of selection is probably involved.

Two of the five individuals are sibs and show the usual features found in childhood. The deletion is of one-third of the short arm (Fig. 1d). Their mother and her sister proved to be balanced translocation heterozygotes (Fig. 2). ASG banding showed that the translocation involves the long arm of No. 7 chromosome, 46,XX,t(5,7)(p13 or 14;q35 or 36). The deleted material includes bands 5p14 and p15 supporting the suggestion of Niebuhr (1972) that these are consistently lacking in this syndrome.

The frequency of the *cri du chat* syndrome in the N.E. region of Scotland, therefore, is approximately 1 in 100 000 and compares with a general estimate given by Polani (1969). Familial occurrence as a result of a balanced translocation has been noted before: de Capoa *et al* (1967) found 13%. A translocation between the short arm of No. 5 chromosome and the long arm of a No. 7 has not been reported previously.

46,XX,21q-. A woman born in 1928, when her mother was aged 37 and her father 48, had a deletion (45%) of the distal region of the long arm of chromosome 21 (Fig. 3a). Translocation of the long arm material was not revealed by ASG banding. She was 148 cm in height and had an IQ of 37 (W.A.I.S.). The head was small (circum. 56 cm), with low set ears, slit-like palpebral fissures, hypertelorism, and a prominent chin. Muscle tone was increased, and there was a pronounced flexion deformity of all the fingers, predominantly at the proximal interphalangeal joints. The carrying angles were increased, while the toes showed a minor degree of syndactyly.

Microcephaly, hypertonia, growth retardation, and skeletal malformation, have been reported to be associated with a deleted long arm of a G group chromosome (cf. syndrome I of Warren and Rimoin, 1970). Finger flexion has also been noted by others (e.g. Challacombe and Taylor, 1969) so that it may well be part of the syndrome and related to hypertonia.

FIG. 1. Partial karyotypes of four cases of *cri du chat*. (a) Case 1—orcein staining, 30% deletion. (b) Case 2—G-banding, 20% deletion of chromosome 5. The deletion may be intercalary and affects p14–p15. (c) Case 3—(i) orcein staining, 50% deletion; (ii) autoradiography showing late-labelling chromosome No. 5; (iii) G-banding chromosome No. 5. The deletion involves p12–p15. (d) Case 4—G-banding, 30% deletion in one sib of the familial cases der(5,t(5;7)(p13 or 14;q35 or 36)ma.

FIG. 2. Balanced translocation heterozygote. G-banding, 46,XX,t(5,7)(p13 or 14;q35 or 36).

FIG. 3. Partial karyotypes of two cases with deleted autosomes. (a) Deleted long arms No. 21. (b) Deleted short arms No. 18. (i) orcein; (ii) G-banding.

46,XX,18p-. One patient, born in 1940, had a deletion involving most of the short arm of chromosome 18 (Fig. 3b). The rest of the chromosome complement appeared normal. Her birthweight was 1814 g, and maternal and paternal ages were 31 and 30 years, respectively. Though she is retarded

(IQ 43 W.A.I.S.) and of short stature (height 156 cm, span 148 cm), she does not have other features suggestive of the 18p- syndrome. Such variation has been noted previously (Hamerton, 1971). Serum levels of IgA, IgG, and IgM were normal and no organ specific or non-specific antibody was detected. Blood group data (Dr Ruth Sanger, 1973, personal communication) showed no unusual findings.

Her niece is also retarded but, though she shows some features suggestive of 18p- syndrome, banding studies showed a normal karyotype for her as well as for the proband's parents. A detectable translocation is, therefore, not responsible for the familial occurrence of retardation.

There were, therefore, 7 individuals with deletions, comprising 0.25% of the survey. Jacobs *et al* (1974) quote for deletions in the combined series of neonates an incidence of 0.01%. This increase in a retarded population is not surprising since subnormality is well recognized as a feature of many deletion syndromes.

Deletions and duplications of the satellites of the D and G group have not been regarded as abnormal.

II: Supernumerary chromosomes

Nine individuals with an extra, small, morphologically unidentifiable chromosome were found within the survey. The supernumerary chromosome varied between individuals, the longest being the size of an E group chromosome. Two were

acrocentric (Fig. 4a, b), 5 submetacentric (Fig. 4c), and 2 rings (Fig. 4d). Two of these cases showed mosaicism, one ring being present in 75% of the cells, and one submetacentric in 22% of the cells examined.

A feature of 6 of the 9 supernumerary chromo-

somes was the presence of satellites. The two acrocentrics bore satellites on their short arms and 4 of the submetacentrics at the ends of both arms. These showed metaphase association with the normal D and G group chromosomes of the complement as did 1 of the 2 ring chromosomes, and all

FIG. 4. Partial karyotypes of D and G group chromosomes in cases with supernumerary chromosomes showing satellite associations and G-banding. (a) Acrocentric of possible No. 21 origin. (b) Acrocentric of unknown origin (22?). (c) Submetacentric of possible No. 15 origin. (d) Ring of unknown origin.

were presumably involved in the formation of common nucleoli. The remaining metacentric and ring chromosome did not show associations and did not carry observable satellites.

The 9 patients did not exhibit any common phenotype that could be associated with the supernumerary elements. One patient showed some of the clinical features characteristic of Down's syndrome, and G banding suggested that the extra element may have been a No. 21 with a partially deleted long arm (Fig. 4a). In one submetacentric G banding indicated that the extra element was probably derived from a chromosome No. 15 (Fig. 4c). This element closely resembles the supernumerary chromosome reported by Watson and Gordon (1974), who also review 3 other cases of partial trisomy 15, identified by G banding.

There are a number of published reports where extra abnormal small chromosomes have been described either in sporadic cases or in families. In a survey of 1255 retarded individuals, Newton *et al* (1972a) found 4 patients with supernumerary chromosomes which resembled those detected in this survey. In 1, the clinical features were those of the cat's eye syndrome (Schachenmann *et al*, 1965), but in the others no definite syndrome was recognized. In a survey of newborn, Walzer, Breau, and Gerald (1969) reported 3 apparently normal babies who possessed an additional metacentric chromosome, frequently with satellites and showing association with other satellited chromosomes. These newborn cases were included in a combined series tabulated by Jacobs *et al* (1974) where the frequency of supernumerary chromosomes in the newborn was 0.02%. This compares with the frequency of 0.28% in a retarded group studied by Jacobs, Frackiewicz, and Law (1972) and with the 0.32% in the present survey. The newborn survey data taken in conjunction with the surveys of the mentally subnormal suggest that their high frequency in the latter group may well be related to the subnormality.

III: Sex chromosome abnormalities

A. Chromatin positive males. There were 19 males with at least one extra X chromosome. This corresponds to 19/1565 or 12.1/1000 of chromatin positive individuals. Of these, 11 showed 47,XXY chromosomes (7/1000) and a further 4 were mosaic for 46,XY/47,XXY. The remaining 4 comprised 2 with a 48,XXYY karyotype, one with a 48,XXXXY and one mosaic with a 48,XXXXY/49,XXXXXY complement (see Table VI). The mean maternal age of the individuals with 47,XXY chromosomes was 32.3 years and the paternal age 31.8

TABLE VI

SEX CHROMOSOME ABNORMALITIES
IN THE 1565 MALES

Chromosome Constitution	No. of Individuals
47,XXY	6
47,XXY	11
46,XY/47,XXY	4
48,XXYY	2
48,XXXXY	1
48,XXXXY/49,XXXXXY	1
	25 (1.6%)

years. The figures for 3 of the Klinefelter mosaic patients were 34.0 and 37.3, respectively.

Earlier estimates of the frequency of Klinefelter's syndrome in the retarded were based on buccal smear surveys of mental subnormality hospitals. Ferguson-Smith (1966) quoted a frequency for chromatin positive males of 0.84% and Court Brown (1969) of 9.4/1000 on combined series. In a regional survey of hospitals for the subnormal, Hunter (1969) found 0.81% chromatin positive males. More recently, Casey *et al* (1973) using data from a combined series quoted a frequency of 0.9% for all chromatin positive males with 0.6% for those shown to be 47,XXY. The series are not homogeneous, and include, for example, data from the State Institution at Carstairs (Jacobs *et al*, 1968). Nevertheless, there is general agreement that about 0.9% of males in subnormality hospitals are chromatin positive. Most of these have a 47,XXY karyotype and are found in the high grade group. This was the reason Newton *et al* (1972b) suggested for the low frequency, 0.43%, which they found in their survey, where one-third of the male patients had a low IQ (less than 20). In the present series only 4 of the 15 individuals with either XXY or XY/XXY chromosomes had an IQ below 50, supporting the view that most of those who are subnormal will be found in the high grade group. That the actual IQ level is not the only factor involved in placement is shown by the fact that XXY and XY/XXY individuals in the 20 to 49 IQ range are living at home.

Another point is that there were in the subnormality hospitals only 2 XXY and 2 XY/XXY patients out of a total of 421 (0.95%). While 2 XXY individuals were in psychiatric hospitals (Table VII), the remaining 9 were at home (0.96%). The frequency in the 3 groups is, therefore, similar, 4/421 compared with 2/125 and 9/944. However, data regarding the numbers of subnormal XXY individuals, derived solely from surveys of subnormality hospitals, cannot necessarily be used to estimate their numbers among high grade persons in the community. In other areas, different facilities

TABLE VII
CHROMOSOME ABNORMALITIES AMONG MALES IN HOSPITAL

Hospitals	Normal 46,XY	+ 21	Trans- location 21	Defi- ciency	Other Autosomal Abnormalities	47,XXY	47,XYY	Other Sex Chromosome Abnormalities	Total
Subnormality Psychiatric	364 121	50 1	— —	1 —	1 —	4 2	— 1	1 —	421 125
Totals	485	51	—	1	1	6	1	1	546

for identifying and caring for those with high grade deficiency, as well as differing criteria for admission, may render unreliable extrapolation from more easily available inpatient data to the whole group.

Two abnormalities were present in one patient, phenylketonuria with Klinefelter's syndrome and 46,XY/47,XXY mosaicism. It may well be that the former was responsible for his IQ being 52 (W.A.I.S.). This association with Klinefelter's syndrome has been reported previously (Benirschke *et al*, 1962). Another of the mosaic patients also has achondroplasia. These are presumably chance associations.

B: Males with 48 chromosomes. 48,XXXXY.

This patient was born in 1917 and he lives at home, helping occasionally on a farm. His IQ is 58 and his height 180 cm, though he now has kyphosis. He has never shaved. His penis is small, with the soft left testis being 0.5 cm long and the right barely identifiable. There is a moderate amount of pubic hair.

48,XXXXY/49,XXXXY. This patient, born in 1923, has been reported previously by Court Brown *et al* (1964) as MRC 186/60. His IQ was 41 and his height 179 cm. No testes were palpable. Obvious prognathism was present.

48,XXYY. Two individuals were identified, the first having also been reported by Court Brown *et al* (1964) as MRC 15/61. Both are now living at home, though the first has a criminal record. Their IQ's are 52 and 47, respectively, with heights of 179 cm and 181 cm. Both have gynaecomastia and small soft testes.

C: Males with 47,XXY chromosomes. Six XYY individuals were identified. One, an inpatient in a psychiatric hospital, was admitted many years ago with a psychotic illness. He has always been termed retarded but such was his skill in evading testing that it made the psychologist suspect a low normal IQ. The other 5 had all attended the local special school for the educationally subnormal.

Their IQs when originally tested fell into the high grade group, though later detailed testing indicates that 2 could be more properly placed in the low normal range.

Of the 3 adults, 2 were 182 cm and the third 191 cm.

The mean paternal age was 31.0 years and maternal age 26.8 years. Further clinical and psychological details have been reported (Clark and Johnston, 1974).

D: Females with sex chromosome anomalies. 47,XXX. Five individuals were detected giving a frequency of 5 in 1205, 4.2/1000. This agrees with previous reports of an increased frequency among the mentally subnormal, e.g. 3.95/1000 by Hamerton (1971), 4.3/1000 by Barr *et al* (1969), and 4.6/1000 by Maclean *et al* (1968).

The youngest menstruates regularly, but reliable information is not available for the others who are post-menopausal. They are all stated to have menstruated. The IQ of the youngest when retested after attending the special school was over 70. Three fell in the 50 to 70 range and one was under 50. This conforms to previous findings that when these individuals are retarded they are usually high grade (Barr *et al*, 1969). Of the 5, 3 were in institutions (Table VIII) and the mean maternal and paternal ages for all 5 were 31.0 and 36.7 years.

48,XXXX. This woman, born in 1936, lives with her widowed father and helps about the house. She has once required admission to a psychiatric hospital when a diagnosis of schizophrenia was made. Her mother had chronic schizophrenia, eventually requiring permanent hospitalization. Her IQ was originally estimated as in the 20 to 50 range (W.A.I.S. 47). When retested, scores between 48 and 86 were recorded and the psychologist noted that the findings were not typically subnormal, but more representative of a moderately stabilized post-psychotic. He regarded the best estimate of her IQ as being 70. Menstruation was said to occur regularly. Her mother was aged 33 and her father 41 at her birth.

TABLE VIII
CHROMOSOME ABNORMALITIES AMONG FEMALES IN HOSPITAL

Hospitals	Normal 46,XX	+ 21	Translocation 21	Deficiency	Other Autosomal Abnormalities	47,XXX	Total
Subnormality Psychiatric	287 100	22 2	— —	1 —	1 —	1 1	312 103
Totals	387	24	—	1	1	3*	415

* One in a cottage hospital.

In her buccal smear 36% of the cells were doubly chromatin positive and 4% triple chromatin positive. Day, Lawson, and Wright (1964) found one 48,XXXX individual among 1088 retarded females, which is comparable with our series.

Conclusions

Total ascertainment of all mentally retarded persons was undertaken for the area served by the former North-Eastern Regional Hospital Board. Chromosome studies were completed in 2770 of the

3020 identified (91.7%), and 1808 of these were living at home on the survey reference date (1 March 1968). So far as we are aware, this is a unique survey of a total population of retarded individuals.

Of the total, 297 (10.7%) were shown to have a chromosome abnormality and of these Down's syndrome accounted for 250 (9%). A D/G or G/G translocation was present in 2% of the Down's cases, and mosaicism of the 46/47 +21 type was present in 4% of the cases. The sex ratio in the Down's patients showed an obvious excess of males.

Five patients with a deleted short arm of No. 5

TABLE IX
INCIDENCE OF CHROMOSOME ANOMALIES IN A SCOTTISH NEWBORN POPULATION (Jacobs *et al*, 1974)
AND IN THE PRESENT SERIES OF MENTALLY RETARDED

<i>Sex chromosome anomalies</i> I. Males	XYX	XXY	XXY Mosaics	Other	Total	
Edinburgh newborn	0.13%	0.11%	0.026%	0.036%	0.30%	
Subnormality survey	0.38%	0.70%	0.26%	0.26%	1.60%	
II. Females	XXX		Other	Total		
Edinburgh newborn	0.13%		0.05%	0.18%		
Subnormality survey	0.42%		0.08%	0.50%		
<i>Autosomal anomalies</i> III. Trisomies	+ E	+ G	Other	Total		
Edinburgh newborn	0.02%	0.15%	0.01%	0.17%		
Subnormality survey	—	9.0%	—	9.0%		
IV. Aneuploidy with rearrangements	Robertsonian Translocations	Reciprocal Translocations	Deletions	Super- numeraries	Other	Total
Edinburgh newborn	0.01%	—	—	0.01%	0.02%	0.04%
Subnormality survey	0.18%	0.07%	0.18%	0.32%	—	0.75%
V. Euploidy with rearrangements	Robertsonian D/G, G/G translocations		Reciprocal translocations	Inversions	Total	
Edinburgh newborn	0.08%		0.09%	0.02%	0.19%	
Subnormality survey	—		—	—	—	

chromosome were identified. One patient with a 46,18p- complement and one with a 46,21q- anomaly were detected. There were 9 individuals with an additional (supernumerary) unidentified chromosome which is probably related to their retardation.

Increased numbers of sex chromosome anomalies among high grade, mentally subnormal individuals of both sexes were confirmed. There were 25 males (1.6%); 6 were 47,YYY, 11 were 47,XXY, 4 were 46,XY/47,XXY, and 4 had 48 or 49 chromosomes. Of the 25, only 7 (including one XYY) had an IQ below 50. One 48,XXXY and one 48,XXYY also had IQ's above 50 and, together with the other 48,XXYY, were living in the community. Only 5 chromatin-positive individuals were in subnormality hospitals, a further 2 were in psychiatric hospitals, while 12 were living at home. Extrapolation of data derived solely from subnormality hospitals regarding the numbers of individuals with Klinefelter's syndrome in the community should, therefore, be approached cautiously.

Additional X chromosomes were found in 6 females (0.5%), 1 with 48,XXXX and 5 with 47,XXX. The former and one of the latter had an IQ below 50.

This survey has shown that chromosome abnormalities contribute significantly to the causation of mental retardation. Down's syndrome provides the most easily recognizable syndrome, but others can sometimes be identified by careful examination. The striking increase of constitutional chromosome anomalies among the mentally retarded is perhaps best seen in comparison with the incidence of chromosome anomalies in the unselected live newborn, where allowance must be made for the high infant mortality in the autosomal trisomies. A summary of the data is compared in Table IX with those recently reported for an Edinburgh series of live-born babies (Jacobs *et al*, 1974).

Table IX shows that among the sex chromosome abnormalities, Klinefelter's syndrome has the greatest liability to retardation (approximately a sevenfold increase) while there is a threefold increase in the 47,YYY and 47,XXX individuals. Among the autosomal anomalies, the well-established large increase in the incidence of trisomy, and mosaic trisomy, G, characterizing the Down's syndrome patients, and the aneuploid rearrangements (deletions) associated with the *cri du chat* syndrome is evident. There is a very significant (a thirtyfold) excess of individuals with an additional small supernumerary chromosome. Aside from mental retardation, the supernumerary chromosomes do not appear to be associated with any other charac-

teristic phenotype. One negative finding worthy of comment is the absence of euploid structural rearrangements of the autosomes in our series. Jacobs *et al* (1974) detected such rearrangements in 0.19% of the newborn population and had previously reported an incidence of 0.33% in postnatal populations, including their retarded groups (Jacobs *et al*, 1972). The failure to detect such anomalies in our series was surprising and whether this was the result of chance, technical reasons, or is of biological significance, is not known.

This study was carried out in co-operation with the University Departments of Mental Health, Community Medicine, and Chemical Pathology in Aberdeen.

Dr Dorothy Younie obtained most of the clinical data and blood samples. Without her enthusiasm and skill this study would not have been possible. Drs Margaret Anderson and Elizabeth Law obtained the remainder of the samples and data, and Miss Eileen McLaughlin provided technical assistance in the early part of the survey. Invaluable secretarial support was supplied by Mrs A. Ross. The help of many others is gratefully acknowledged, particularly the family doctors and the staff of the Regional Service for the Mentally Handicapped.

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