A 3-year cytogenetic survey of 9 661 patients in South Africa

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Summary

During the period 1 January 1977 - 31 December 1979, 9 661 patients underwent cytogenetic investigation at seven participating laboratories in South Africa. The chromosome data were coded using a standard protocol and the results tabulated, being listed according to the clinical signs which led to referral for investigation.

Cytogenetic investigation was most commonly requested for prenatal studies, and 22% of the group's effort was directed towards this. One in 27 amniotic cell specimens was reported to have shown anomalous chromosomes, trisomy 21 being the most frequent abnormality.

The majority of postnatal investigations were requested because congenital abnormalities suggested an underlying chromosomal defect. In 42,3% of 2 420 patients a chromosome defect was confirmed. Results of chromosome studies are tabulated by indication for referral and the findings summarized.

This collaborative study gives an indication of the nature and frequency of chromosome disorders in South Africa.

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Correct diagnosis leads to informed prognosis and improved management of patients. In many instances of congenital defects and dysmorphology knowledge of the chromosomal status of the patient provides the necessary information for the making or confirmation of a diagnosis.

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The expanding use of cytogenetic investigations by clinicians has been obvious during the last decade, and this demand has resulted in cytogenetic laboratories being established in the major centres throughout the RSA. In 1976 the Human Cytogenetic Study Group was formed,[1] one of its aims being the collation of results from all diagnostic laboratories in this country in order to assemble data pertaining to cytogenetic problems in South Africa. During the following 3 years the results of chromosome studies carried out by the collaborating laboratories were coded and submitted to the Department of Cytogenetics of the University of Stellenbosch for computer analysis. This is a report of the combined data.

Protocol

During the period 1 January 1977 - 31 December 1979 a total of 9 661 patients were successfully karyotyped by the group. Each laboratory supplied relevant information about the patient and the chromosome findings; patients were identified by laboratory accession number and initials only. The data were coded by the contributing laboratories using a standard protocol[2] to ensure that details from each centre were comparable, and a Hewlett Packard 2 100 computer was used for the compilation of data sets employing the format described previously.[2] Results were tabulated by programme STAT9A.

Results

Chromosomal abnormalities were detected in 1 807 patients (18,7%). The results are tabulated and discussed in categories based on the primary clinical indication for chromosome studies as supplied by the referring doctor (Table I). In many instances the clinical signs supplied did not support the stated diagnosis, and this fact explains many of the discrepancies between reasons for referral and the karyotypes.

Congenital abnormalities

According to the clinical information supplied, 1 386 patients were investigated because Down, Edwards' or Patau's syndrome was diagnosed. A further 1 034 patients without specific features of any particular syndrome were classified as having 'nonspecific' congenital abnormalities.

Down syndrome was the clinical diagnosis in 1 211 cases (Table II), of which 820 (68%) were found to have abnormal chromosome constitutions; of these, 729 (89%) had the common, non-disjunctional trisomy 21 and 47 (5,7%) had mosaic karyotypes that included a normal cell line. Unbalanced translocations were identified in 35 patients with trisomy 21; chromosome 14 was involved in 15 of 18 identified D/G translocations. Two patients were found to have trisomy X in addition to trisomy 21. Abnormalities of chromosomes other than 21 were seen in 9 patients. One-third of the patients referred with a suspected clinical diagnosis of Down syndrome had a normal karyotype with no detectable mosaicism.

TABLE I. CHROMOSOME FINDINGS IN 9 661 PATIENTS BY INDICATION FOR REFERRAL

Indication	Karyotype		
	Normal	Abnormal	Total
Congenital malformations			
Down syndrome	391	820	1 211
Edwards' syndrome	67	67	134
Patau's syndrome	26	15	41
Nonspecific	913	121	1 034
Total	1 397	1 023	2 420
Anomalous sex determination or development			
Primary amenorrhoea	220	55	275
Secondary amenorrhoea	120	4	124
Oligo-amenorrhoea	20	0	20
Male infertility	211	8	219
Turner's syndrome	193	110	303
Klinefelter's syndrome	193	54	247
Ambiguous external genitalia	202	9	211
Others	365	24	389
Total	1 524	264	1 788
Prenatal chromosome studies	2 071	79	2 150
Myelo- and lymphoproliferative disorders	334	250	584
Chromosome breakage syndromes			
Ataxia telangiectasia	1	3	4
Fanconi's anaemia	20	27	47
Products of conception	12	2	14
Mental retardation	314	17	331
Radiation exposure	5	0	5
Repeated miscarriage	271	5	276
Retarded growth	94	8	102
Viral infection	1	0	1
Family studies	1 537	113	1 650
Unclassified — insufficient clinical details	273	16	289
Grand total	7 854	1 807	9 661

Edwards' syndrome was diagnosed in 134 patients, but only 67 were confirmed as having trisomy 18; this figure included 3 patients with mosaicism for a normal cell line and 1 with an unbalanced 18/21 translocation. Structural and other chromosome defects are listed in Table III.

Patau's syndrome was suspected in 41 patients, 15 of whom were found to have abnormal karyotypes (Table IV). Six had trisomy 13, 5 having unbalanced translocations involving chromosome 13, and 4 had chromosome abnormalities not involving chromosome 13.

Nonspecific congenital abnormalities not suggestive of the well-known trisomy syndromes mentioned above occurred frequently, but only 121 of the 1 034 patients (12%) in this category were found to have abnormal chromosome constitutions (Table V), the majority showing miscellaneous structural rearrangements which resulted in partial monosomies or trisomies. Trisomies of chromosomes 13, 18 and 21 appeared less commonly and sex chromosome abnormalities were few in this category.

Abnormalities caused by trisomy 13, 18 or 21 clearly do not always suggest the expected syndromes (see Tables II-V, IX). In Table VI the total numbers of subjects with these common autosomal trisomies are shown, disregarding the clinical indication for investigation. It is interesting to note that in the group with trisomy 13 one-third of the patients had unbalanced translocations involving chromosome 13. The preponderance of females is a feature of those with trisomy 18, the ratio here being 4:1.

Anomalous sex determination or development

Disorders of sex determination or development were classified according to their presenting features as: amenorrhoea, infertility, Turner's and Klinefelter's syndromes, and ambiguous genitalia or other contrasexual signs.

Amenorrhoea was the reason for referral in 419 patients (Table VII). Of 275 patients with primary amenorrhoea, 55 (20%) had an anomalous or inappropriate karyotype; 50% of these patients' karyotypes showed numerical abnormalities and the remainder had structural abnormalities of the X chromosomes. Male sex chromosomes (XY) were found in 12 of these phenotypic females, indicating discrepancies between genotype and phenotypic development. Only 3% of patients with secondary amenorrhoea had abnormal chromosomes, while in the small group with oligomenorrhoea no abnormal chromosomes were seen. Three patients had unusual translocations involving an X chromosome and an autosome.

Male infertility (Table VIII) is not often associated with chromosomal defects; although the frequency is high in azoospermic patients, they are a minority in this category.

Turner's and Klinefelter's syndromes are commonly diagnosed (Table IX); of patients referred for confirmation of Turner's syndrome, 36% had monosomy or structural changes of the X chromosome, frequently in mosaic form (39%). Of 247 patients thought to have Klinefelter's syndrome, 54 had abnormal karyotypes, in most cases due to the presence of additional sex chromosomes. Four of these patients proved to be XX males.

TABLE II. CHROMOSOME FINDINGS IN 1 211 PATIENTS WITH DOWN SYNDROME

Karyotype		
Normal (46,XX or XY)		391 (32%)
Abnormal		820 (68%)
Numerical		
Non-disjunction*		
47,+21	726	729 (89,0%)
48,+21,+X	2	
48,+21+mar	1	
47,+13	1	4 (0,5%)
47,+18	3	
Mosaics†		
46/47,+21		47 (5,7%)
Structural trisomy		
46,t(13/21)	1	23 (2,8%)
46,t(14/21)	15	
46,t(15/21)	2	
46,t(D?/21)	5	
46,t(21/21)	7	12 (1,4%)
46,t(21/22)	4	
46,t(G?/21)	1	
Other structural defect		
46,del(5p)	1	5 (0,6%)
47,+fra	1	
47,+mar	1	
46,dup 21q11-q22	2	

*Prezygotic origin — meiotic failure.
†Postzygotic origin — mitotic failure.

TABLE III. CHROMOSOME FINDINGS IN 134 PATIENTS WITH SIGNS OF EDWARDS' SYNDROME

Karyotype	No. of patients
Normal (46,XX or XY)	67
Abnormal	67
Numerical	
47,+18	53
46/47,+18	3
47,+13	2
47,+D	2
47,+21	1
47,+22	1
Structural	
46,r(18)	1
46/46,r(18)	1
46,t(18/21) unb	1
46,t(3,4)	1
46,del(5p)	1

TABLE IV. CHROMOSOME FINDINGS IN 41 PATIENTS WITH SIGNS OF PATAU'S SYNDROME

Karyotype	No. of patients
Normal (46,XX or XY)	26
Abnormal	15
Numerical	
47,+13	6
47,+18	2
47,+21	1
Structural	
46,t(12/14)	1
46,t(13/13)	3
46,t(13/14)	2

TABLE V. CHROMOSOME FINDINGS IN 1 034 PATIENTS WITH NONSPECIFIC CONGENITAL MALFORMATIONS

Karyotype	No. of patients
Normal (46,XX or XY)	913
Abnormal	121
Numerical	
47,+13	8
47,+18	20
47,+21	10
Structural trisomy	
46,t(13/14)	3
46,t(21/21)	2
Other structural	78

TABLE VI. SUMMARY OF 935 CASES IN WHICH CHROMOSOMES 13, 18 OR 21 CAUSED CONGENITAL MALFORMATIONS

Karyotype		No.
Chromosome 13		
47,+13		**18 (69,2%)**
46,t(13/13)		**3 (11,5%)**
46,t(13/14)		**5 (19,2%)**
		26 (100%)
Chromosome 18		
47,XX,+18	62	**(95,1%)**
47,XY,+18	16	
46/47,+18		**3 (3,7%)**
46,t(18/21)		**1 (1,2%)**
		82 (100%)
Chromosome 21		
47,+21		**738 (89,2%)**
46,t(13/21)	1	**23 (2,8%)**
46,t(14/21)	15	
46,t(15/21)	2	
46,2(D?/21)	5	
46,t(21/21)	9	**14 (1,7%)**
46,t(21/22)	4	
46,t (G?/21)	1	
46/47,+21		**47 (5,7%)**
46,dup(21)	2	**5 (0,6%)**
48,+21,+X	2	
48,+21,+mar	1	
		827 (100%)

Ambiguous external genitalia or other abnormal sex characteristics led to the investigation of 600 patients (Table IX). Interesting chromosomal anomalies were revealed in 9 of 211 with ambiguous external genitalia; 4 were chimaeras, 3 having XX/XY mosaicism and 1 a 46/69 mosaic karyotype. A further 389 patients had abnormal sex characteristics but they could not be classified because insufficient clinical details were supplied. Contradictory sex chromosome complements were found in 11 phenotypic females and 5 phenotypic males. Eight other patients in this group revealed a variety of abnormal karyotypes.

Prenatal chromosome studies

A total of 2 150 amniotic cell cultures were examined (Table X) and chromosome abnormalities were reported in 79 (3,7%). Non-mosaic non-disjunction led to numerical discrepancies in 41 of these, trisomy 21 being very much commoner than any

TABLE VII. CHROMOSOME FINDINGS IN 419 PATIENTS INVESTIGATED BECAUSE OF AMENORRHOEA

Karyotype	No. of patients	
Primary amenorrhoea		
Normal (46,XX)		220
45,X	7	
45,X/46,XX	7	
47,XXX	1	19
46,XX/47,XXX	3	
45,X/46,XX/47,XXX	1	
46,X,del(Xp)	1	
46,X,del(Xq)	2	
46,X,del(Xp)	1	
46,X,dic(X)	1	
46,X,i(Xq)	7	19
46,XX/46,X,i(Xq)	3	
46,XX/46,X,r(X)/46,X,del(Xq)	1	
46,X,t(X;2)bal	1	
46,X,t(X;7)	1	
46,XX,t(14;17)bal	1	
45,X/46,X,+mar	1	
45,X/46,X,r(X)	1	
46,XX/47,XX,+mar	1	5
45,X/46,X,del(Xq)	1	
45,X/46,XX/46,X,del(Xq)	1	
46,XY		12
Secondary amenorrhoea		
Normal (46,XX)		120
46,X,del(Xq)	1	
46,X,i(Xq)	1	4
45,X/46,X,del(Xp)	1	
46,X,t(X;2;15)	1	
Oligomenorrhoea		
Normal (46,XX)		20

TABLE VIII. CHROMOSOME FINDINGS IN 219 INFERTILE MALES

Karyotype	No. of patients
Azoospermia	
Normal (46,XY)	16
47,XXY	4
Oligospermia	
Normal (46,XY)	135
46,XY,t(7;15) bal	1
Primary infertility	
Normal (46,XY)	60
47,XXY	1
46,XY/47,XY,+mar	1
46,XY,t(1;3) bal	1

other problem. Fourteen of 16 cases showing structural changes in the chromosomes had balanced translocations. Mosaicism was noted in 14 cultures but 4 of these were artefacts which arose in culture. In 8 cases chromosome breakage, fragments, or apparently normal variants were reported.

Myelo- and lymphoproliferative disorders. Acquired chromosome abnormalities were detected in 250 of 584 patients referred for investigation of various haematological disorders (Table I). The Philadelphia (Ph^1) chromosome was observed in 165 patients with abnormal karyotypes; in those that were banded the majority were identified as t(9;22). A high proportion

TABLE IX. CHROMOSOME FINDINGS IN 1 150 PATIENTS WITH CLINICAL FEATURES OF TURNER'S OR KLINEFELTER'S SYNDROME OR GENITAL AMBIGUITY

Karyotype	No. of patients	
Turner syndrome		
Normal (46,XX)		193
45,X	51	
45,X/46,XX	14	73
Other mosaics	8	
46,X,iso(Xq)	7	16
Other structural defects	9	
45,X/46,X,iso(Xq)	8	21
45,X/structural defects	13	
Klinefelter syndrome		
Normal		193
47,XXY	37	
47,XYY	4	
46,XX	4	
48,XXXY	1	54
47,XY,+mar	1	
46,XY/47,XXY	5	
48,XXYY	2	
Ambiguous external genitalia		
Normal (XX or XY)*		202
45,X/46,XY	1	
45,X/46,X,dic(Y)	1	
45,X/46,X,del(Xq)	1	
46,X,del(Yq)	1	9
46,XX/46,XY	3	
46,XX/69,XXY	1	
47,XY,+13	1	
Other anomalous sex characteristics		
Normal		365
46,XY female	11	
46,XX male	5	
47,XXX	1	
48,XXXY	1	24
45,X/46,XX	3	
45,X/46,XY	1	
45,X/46,XY	1	
46,XY/47,XXY	1	

*See text for discussion.

of the other 85 subjects with chromosome abnormalities showed non-random clonal defects associated with acute leukaemia and other myeloproliferative disorders.

Chromosome breakage syndromes. Three of 4 patients with clinical indications of ataxia telangiectasia were found to have an abnormally high percentage of chromosome breaks, and 27 of 47 patients with Fanconi's anaemia also showed the expected high proportion of breaks in cultured lymphocyte chromosomes.

Other reasons for referral. Substantial numbers of cytogenetic studies were carried out for diverse reasons (Table I) but generally with small reward; 289 specimens were received with so little clinical information about the patients concerned that they could not be classified into any of the categories used in this study.

Family studies. Chromosome rearrangements were reported in 113 (7%) of 1 650 relatives of index patients in whom the abnormality was first detected.

Cytogenetic studies performed in the neonatal period. To give an indication of the age at which various defects are investigated in clinical practice, infants aged up to 1 year encoun-

TABLE X. CHROMOSOME FINDINGS IN 2 150 AMNIOTIC CELL PREPARATIONS

Karyotype	No. of patients
Normal (46,XX or XY)	**2 071**
Numerical defects	
47,+21	**26**
47,XXY	**4**
47,XXX	**4**
47,+13	**1**
47,+18	**3**
47,+mar	**2**
45,X	**1**
46,XX/46,XY*	**3**
46,XX/47,XXX	**2**
46,XX/47,XX,+2*	**1**
46/47,+18	**1**
46/47,+21	**3**
46/47,+mar	**2**
46,X,i(Xq)/47,XXX	**1**
48,XXX,+del(18q)mat	**1**
	55
Structural defects	
Balanced translocations	**14**
Unbalanced translocations	**2**
	16
Variant chromosomes, fragments, breakages	**8**

**In vitro* phenomena — see text.

tered in this sample are listed (Table XI). Many subjects with Down syndrome (77%) are identified in this period, as are almost all of those with the severe malformations of Patau's and Edwards' syndromes. Nonspecific congenital abnormalities are less likely to be investigated during the neonatal period — one-third were not. A significant observation is that barely 50% of the subjects with genital ambiguity were referred for cytogenetic studies at this early age.

Discussion

During the period 1 January 1977 - 31 December 1979 cytogenetic investigations were completed in 9 661 patients by the seven participating diagnostic laboratories in South Africa. The results demonstrate the frequencies of chromosomal anomalies in different clinical problems; from this the importance of cytogenetic studies can be assessed.

Cytogenetic investigation was most commonly requested for prenatal diagnosis, and almost one-quarter of the study group's efforts were directed towards this. Prenatal chromosome studies are expensive and demanding of technologists' time, but the results justify the investment; in 1 of 27 prenatal studies abnormal chromosomes were reported, trisomy 21 being the most frequent. Of the 79 abnormalities reported, about 50 would have been serious enough to warrant a therapeutic abortion (1/43 cases). Artefacts which arose in culture were reported in only 4 of the more than 2 000 amniotic cell cultures, a reassuringly low frequency. In 3 instances it appeared that maternal cells had persisted in culture to produce spurious XX/XY mosaicism, and in the other case mosaicism involving a clone with trisomy 2, a lethal condition *in vivo*, could be discounted as having arisen *in vitro*.

Postnatal chromosome studies were mainly requested because congenital malformations suggested an underlying chromosomal cause. In 58% of these cases a particular syndrome was indicated, and in almost two-thirds (64,7%) a chromosome defect was confirmed. However, in a large group with multiple congenital abnormalities not suggesting a specific syndrome the frequency of chromosome defects was quite low (12%).

In each of the autosomal trisomy syndromes and the group with nonspecific malformations several patients were found to have karyotypes that did not correspond with the stated diagnosis, or, in the nonspecific group, karyotypes that should have been associated with a recognizable phenotype. This suggests that not all medical practitioners are familiar with even the commoner chromosomal syndromes. Five subjects stated to have Down syndrome had karyotypic abnormalities involving chromosomes other than 21, but there was relatively more uncertainty when the provisional diagnosis of Patau's (trisomy 13) or Edwards' (trisomy 18) syndrome was indicated; 10 of the 175 patients in these categories had unexpected chromosome anomalies. Also, the lower proportions of patients in these groups who proved to have abnormal karyotypes (36,5% and 50% respectively, compared with 67,7% in the group with Down syndrome) is evidence that phenocopies of these multiple congenital malformation syndromes are common. The most varied and unusual chromosome defects were found in patients with nonspecific, multiple malformations.

TABLE XI. SUMMARY OF CHROMOSOME FINDINGS IN 2 129 INVESTIGATIONS OF NEONATES DURING THE SURVEY PERIOD

	Karyotype		
Reason for referral	Normal	Abnormal	Total
Congenital malformations			
Down syndrome	**272**	**669**	**941**
Edwards' syndrome	**66**	**65**	**131**
Patau's syndrome	**25**	**15**	**40**
Nonspecific	**601**	**89**	**690**
Total	**964**	**838**	**1 802**
Anomalous sex determination or development			
Turner's syndrome	**53**	**20**	**73**
Klinefelter's syndrome	**3**	**1**	**4**
Ambiguous external genitalia	**118**	**3**	**121**
Other	**79**	**2**	**81**
Total	**253**	**26**	**279**
Retarded milestones	**46**	**2**	**48**
Grand total	**1 263**	**866**	**2 129**

Prezygotic non-disjunction resulting in trisomy is clearly the major cause of numerical anomalies; postzygotic non-disjunction, the origin of mosaic karyotypes, is a relatively uncommon event and accounts for only about 6% of autosomal trisomies. Double aneuploidy occurred in 3 patients with Down syndrome, demonstrating that the autosomal trisomy dictates the appearance of the phenotype. Translocations occurred in 4,5% of the subjects with trisomy 21 and this is significant because it is important that parents, and possibly other relatives, of subjects with translocation chromosomes also be investigated in order to detect clinically normal translocation carriers. Prenatal investigation of pregnancies in such people is strongly indicated.

Another feature of these results is the high prevalence of mosaicism in karyotypes showing sex chromosome aneuploidy. In the group with Turner's syndrome 43 of 110 (39%) abnormal karyotypes had two or more cell lines. Similarly, of 55 patients with primary amenorrhoea and associated abnormal karyotypes, 20 (36%) were mosaic. By comparison, autosomal mosaicism is unusual. Three amenorrhoeic women in this series had X/autosome translocations. Such rearrangements are very uncommon.[3]

It is surprising that only 9 of the 211 individuals with ambiguous genitalia were found to have abnormal karyotypes. This is not to say that the remaining 202 patients had appropriate sex chromosome complements; histological examination of gonadal tissues, essential to the establishment of the diagnosis in such cases, if in fact this was done, was not reported in this survey.

Males with infertility other than that caused by azoospermia usually had normal karyotypes. Similarly, mental retardation alone, the reason for referral in 3,4% of the sample, was not often associated with chromosomal defects. It should be noted, however, that this survey was carried out before the fragile X chromosome had been reported in male retardates. The low frequency of chromosome abnormalities in the group complaining of repeated abortions (5/276) was in keeping with data reported from other countries.[4] The high prevalence of chromosome aberrations in myeloproliferative disorders, Fanconi's anaemia and ataxia telangiectasia is confirmed here. The identification of specific acquired chromosome abnormalities in myelo- and lymphoproliferative disorders has led to new concepts of the aetiology of these conditions, and will hopefully be of practical use to clinicians in making a diagnosis, evaluating the patient's response to therapy, detecting relapses, and making the prognosis for survival.

One of the more positive aspects of cytogenetic investigations in medical practice is the fact that if a particular chromosome disorder is identified in a proband, it is possible to investigate those of the relatives who may also be at risk of producing abnormal offspring. Seventeen per cent of the sample were referred for karyotyping in the course of family studies, and 113 were found to be carriers of anomalous chromosomes. In such cases genetic counselling may be offered and, where indicated, prenatal investigation may be recommended, with a clear indication to the laboratory of which specific chromosome abnormality is to be sought.

In South Africa there are only limited facilities for cytogenetic investigations, and these tests are costly; however, the value of proper diagnosis in the management of affected individuals is incalculable, and the savings in time and money of caring for people handicapped by congenital disorders far outweigh the costs of prenatal detection. In this collaborative study the results have been grouped according to the primary reasons given by the attendant doctors for requesting investigation; these were not always correct, but nevertheless the data given here provide an indication of the nature and frequency of chromosome disorders in this country. Further analysis of these data may indicate topics for detailed study and be useful in planning the future provision of cytogenetic diagnostic laboratories and those services involved in the care and treatment of affected people.

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