3. D. S. Fredrickson, R. I. Levy, R. S. Lees, *New Eng. J. Med.* **276**, 32 (1967).
4. F. T. Hatch and R. S. Lees, *Adv. Lipid Res.* **6**, 1 (1968).
5. R. J. Havel, H. A. Eder, J. H. Bragdon, *J. Clin. Invest.* **34**, 1345 (1955); D. G. Cornwell, F. A. Kruger, G. J. Hamwi, J. B. Brown, *Amer. J. Clin. Nutr.* **9**, 41 (1961); N. Spritz and M. A. Mishkel, *J. Clin. Invest.* **48**, 78 (1969); R. S. Lees and F. T. Lindgren, in preparation.
6. R. S. Lees and E. H. Ahrens, *N. Eng. J. Med.* **280**, 1261 (1969); R. S. Lees, *Circulation* **40** suppl. 2, 15 (1969). The immunoassay was carried out with 1 percent agarose gel, into which LDL diffuses readily (*4*).
7. Since chylomicrons and VLDL share common antigenic determinants with LDL (*3*, *4*), it is essential to remove them before LDL immunoassay. This is conveniently done without altering LDL concentration as outlined in (*4*, p. 31).
8. This group included 9 samples from men and 11 from women. Four of the plasma samples were from normal subjects, 1 each from subjects with types I, II, and III, 5 from subjects with type IV and 7 from those with type V lipoprotein patterns. The group was so selected in order to have representation of all levels of plasma glycerides from $<$ 50 to $>$ 5000 mg/100 ml.
9. O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. T. Randall, *J. Biol. Chem.* **193**, 265 (1951). The results were corrected for the greater color yield of LDL relative to the bovine albumin standard, as suggested by S. Margolis and R. G. Langdon, *J. Biol. Chem.* **241**, 469 (1966).
10. I thank W. M. Rand, of the Department of Biostatistics, Massachusetts Inst. of Technology, for the statistical analysis. The techniques used were those described by T. W. Anderson, *Introduction to Multivariate Statistical Analysis* (Wiley, New York, 1958).
11. J. L. Oncley, F. R. N. Gurd, M. Melin, *J. Amer. Chem. Soc.* **72**, 458 (1950); E. P. Smith, *Lancet* **1962-II**, 530 (1962); D. G. Cornwell, in *Lipids and Lipidoses*, G. Schettler, Ed. (Springer-Verlag, Berlin, 1967), p. 168.
12. D. S. Fredrickson, R. I. Levy, F. T. Lindgren, *J. Clin. Invest.* **47**, 2446 (1968).
13. J. H. Bragdon, E. Boyle, R. J. Havel, *J. Lab. Clin. Med.* **48**, 43 (1956).
14. R. A. Heinle, R. I. Levy, D. S. Frederickson, R. Gorlin, *Amer. J. Cardiol.* **24**, 178 (1969).
15. I thank Dr. E. H. Ahrens, Jr., in whose department at the Rockefeller University this work was begun, for support, and Miss Carolyn Flowers for technical assistance. This study was supported in part by PHS grants (HE 06222, HE 12621, FR 00088 and FR 00102) and in part by grants from the American Heart Association (69-714) and the Burroughs Wellcome Fund.

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Chromosomal Abnormalities in the Human Population: Estimation of Rates Based on New Haven Newborn Study

Abstract. *The incidence of gross chromosomal abnormality was measured in a large (4500), relatively unbiased sample of New Haven infants born during 1 year. The frequency of infants with abnormal chromosomal constitutions was 0.5 percent. For mothers over age 34, 1.5 percent of newborns were chromosomally abnormal. Only one in four of these infants could have been detected by phenotypic criteria alone. Methods are discussed whereby this fraction of the newborn population might be detected and possibly reduced.*

The genetic, clinical, and social significance of chromosomal variation in the human population can only be determined by studying a large, unbiased sample. Since it is now possible to determine the karyotypes of fetuses by amniocentesis during the 12th to 16th week of pregnancy (*1*), it is extremely important to know the significance of chromosomal variation. Most cytogenetic studies have been carried out on institutionalized patients or other small, biased populations. The present study is the largest, relatively unbiased survey of the chromosome complements of newborns yet performed. Forty-five hundred infants, born consecutively over 1 year at Yale–New Haven Hospital, were studied. The New Haven area population is approximately 400,000, and the total number of births each year is about 6900. The remaining 2400 babies in the area are born at a second hospital. The major difference between the two neonatal populations is that a larger percentage of Negro infants were born at Yale–New Haven Hospital (18 percent) than were born at the Hospital of St. Raphael (13 percent).

Leukocytes from the cord blood of each infant were grown in vitro and then prepared for cytological examination by methods described elsewhere (*2*). Two cells from each infant were photographed and then idiogrammed according to standard conventions (*3*). In instances where abnormalities were detected, 30 cells were photographed and studied. Complete clinical and sociological data were recorded for each infant and its family. Chromosomal, clinical, and sociological data were coded for computer storage in order to facilitate information retrieval and analysis (*2*).

Table 1. Number of chromosome abnormalities.

Type of abnormality	Chromosomal abnormalities	
	No.	No./1000 births
Translocations	6	1.37
Trisomy D	1	0.23
Trisomy E	1	0.23
Trisomy G	3	0.69
XYY	3	0.69
XXY	4	0.92
XXX	3	0.69
XO	1	0.23

Successful chromosome preparations were obtained from 4366 of 4482 infants included in the study (97.4 percent). Twenty-two infants had a chromosome abnormality (Table 1). Half involved the sex chromosomes and half the autosomes. The overall frequency (1/200) is comparable to other surveys of consecutive newborns (*4*, *5*). Similarly, in these other studies the abnormalities were divided equally between the autosomes and the sex chromosomes. The frequency of 1/200 is a minimum estimate, since our study is based upon a sample of only two cells per newborn and thus does not include mosaics.

Six infants had a translocation, and five had an autosomal trisomy (Table 2). The frequency of XYY karyotypes in male infants was 3 in 2184 in our study, 5 in 3496 in the Edinburgh study (*5*), and 4 in 1066 in the Ontario study (*4*). If these studies of consecutive newborns are pooled, an XYY karyotype occurred once in 570 male births. In a survey of more than 2000 male newborns in Boston (*6*), most of whom were selected because of a normal phenotype, no XYY males were found. Although the frequency of XYY males would be lower if these newborns were included in the calculation, the latter series is not comparable and therefore cannot be considered together with the surveys of consecutive newborns. Whether the variation in frequency of an XYY karyotype in surveys of newborns is due to the relatively small size of each of the surveys or represents a real epidemiological difference is currently unclear. In the present study, an XXY karyotype was present in 1 of 545 male babies. An XXX karyotype occurred once in 727 female newborns, and a 45, X karyotype only once in 2181 female newborns. Trisomy G in our study was less common than reported previously (*7*, p. 150). The maternal age of 25.7 years in the New Haven population was about 2 years lower than that for the total United States, England, and Australia in recent years (*7*, p. 157), and there were only half as many mothers over 34 years in the present study (7.7 percent). The lower incidence of Trisomy G (1/1455) in our study may represent a real difference from the reported frequency of 1 in 600 to 700 in the literature because of the lower maternal age. A similar downward trend in the incidence of Trisomy G in Victoria and England has been reported recently by Collmann and Stoller (*8*).

Six infants were found to have trans-

located chromosomes, of which three were inherited. None of these babies had normal phenotypes, and their birth weights were in the normal range. A definite unbalanced translocation (B/?) was detected in one child and his father, both of whom were normal (Fig. 1). The remaining five were balanced, reciprocal translocations and have been reported in detail elsewhere (*2*). None of these infants with translocations could have been ascertained except by chromosome analysis.

Five infants were found to have trisomy of the D, E, or G groups (Table 2). The phenotypes of these infants were abnormal and consistent with previously reported descriptions of these trisomies. No infants found with autosomal trisomy were normal.

The XYY infants deserve special comment. Two of the three XYY infants had neonatal complications. The first XYY infant was one of two dizygous male premature twins, and had a very low birth weight (1170 g). The only anomaly present was an inguinal hernia. The second XYY infant also weighed less than 2500 g; placental insufficiency and dysmaturity were noted. His course was complicated by apnea, and he was found to have pectus carinatum and strabismus. The third was normal at birth. Each of these three infants, however, are now more than two years of age and doing well. Nine XYY infants have been ascertained in other surveys of newborns (*4, 5*) and all were phenotypically normal. One of these nine, and one of three in the present series were members of dizygous twins, a total frequency of 2 in 12. As suggested recently by Ratcliffe *et al.* (*5*), the frequency of aneuploidy in twins may be increased.

One of the three XXX infants had major congenital anomalies and a low birth weight. None of the four male infants with an XXY karyotype was abnormal or had any neonatal complications, but three of the four had a birth weight less than 2800 g.

The developmental and behavioral patterns of infants with XYY and other aneuploidies of the sex chromosomes were studied at 1 year by an investigator who was not informed of their cytogenetic constitution. Three aspects of the development and phenotype of the infants with abnormalities of sex chromosomes and translocations are of particular importance. None displayed evidence of developmental retardation at 1 year; although a mild degree of retardation could have been missed at this age, it is unlikely that moderate or severe mental retardation is present. None have died. No consistent phenotype was associated with any of these specific abnormalities of sex chromosomes or translocations. These categories of abnormality, therefore, can only be diagnosed by cytogenetic screening.

An effort was made to identify a group of parents with a high risk of having infants with chromosomal abnormalities. The primary finding was a bimodality and increase in maternal age for the mothers of aneuploid children (Table 3). These effects have been well documented for Down's syndrome (*1*, p. 156) and other aneuploidies, but information has not previously been available for the entire group of chromosomally abnormal children. As shown in Table 2, 26 percent of these mothers were over 34, compared to 7.7 percent in the total sample. Moreover, 1.5 percent of children of mothers over 34 were chromosomally abnormal. A similar and probably independent relationship to maternal weight was observed. Eight of 19 mothers (42 per-

Table 2. Clinical and cytogenetic findings in 22 infants with chromosomal abnormalities. M, male; F, female; 1 kg = 2.2 lb.

Type of variant	Phenotypic sex	Birth weight (g)	Maternal		Anomalies and course
			Age	Wt. (lb)	
			Translocations		
D/D	F	3250	24	110	None
*D/D	F	3090	32	135	None
A/G	M	3570	24	141	None
*D/G	M	3600	26	134	None
*B/?	F	3930	26	119	None
A/B	F	3460	24	108	None
			Autosomal trisomy		
D+	F	2010	28	163	Characteristic anomalies (expired)
E+	M	2070	23	112	Characteristic anomalies; still living age 18 months
G+	M	2990	32	145	Characteristic appearance; patent ductus
G+	M	2600	23	93	Characteristic appearance
G+	F	3640	40	113	Characteristic appearance; congenital hip dislocation
				47, XYY	
	M	3470	26	115	None
	M	1170	36	116	? Megalocephaly, inguinal hernia
	M	2370	25	171	Placental insufficiency, pectus carinatum, strabismus
				47, XXY	
	M	2410	23	157	None
	M	2610	27	120	None
	M	2750	38	145	None
	M	3360	36	165	None
				47, XXX	
	F	3300	38	113	None
	F	2160	20	145	Abnormal ears, congenital heart lesion
	F	3560	21	139	None
				45, X	
	F	2680	19	95	None

* One parent with same translocation; other parent's karyotypes normal.

Table 3. Distribution of maternal ages. N = number of abnormalities divided by number in age group.

Age group	Maternal age		Risk of chromosome abnormality by age group	
	Distribution of total sample (%)	Distribution of mothers of children with chromosome abnormality* (%)	N	Percentage
10-14	0.4	0	0/19	
15-19	11.0	5.3	1/490	0.20
20-24	34.4	42.4	8/1531	0.52
25-29	32.0	21.2	4/1423	0.28
30-34	14.3	5.3	1/635	0.16
35-39	6.2	21.2	4/277	1.44
40-44	1.4	5.3	1/62	1.61
45-49	.07	0	0/3	

* Inherited translocations excluded.

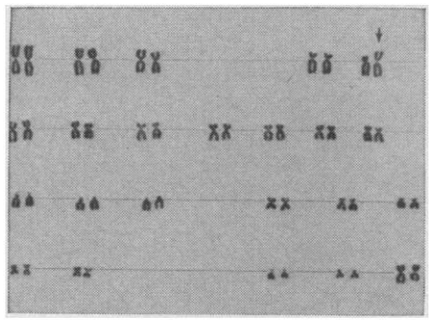

Fig. 1. B/? translocation. In view of the large size of this translocation, it is unlikely that there is an undetected reciprocal translocation although the phenotype of this infant was also normal. The father's autosomal complement was identical.

cent) weighed more than 140 lb (1 kg = 2.2 lb) compared to 27 percent of the total sample of mothers, and the most frequent weight class in the total sample (120 to 139 lb) was the least common in mothers of the chromosomally abnormal children. Since only two of these eight mothers were over 34, the relationship is probably independent of age. Two of the 11 mothers of infants with sex chromosome variants, as well as one mother of an infant with Down's Syndrome, had significant thyroid disease (two hyperthyroid and one hypothyroid) in contrast to 3.7 percent of the overall sample of mothers. The highest risk was found within the group of mothers with thyroid disease, and two of 50 mothers giving a history of hyperthyroidism had chromosomally abnormal children, a risk of 4 percent. Neither of the latter relationships should be regarded as more than possible clues, however, in view of the small sample size. Several negative findings are of equal interest. For mothers in the total sample and for those with chromosomally abnormal infants, the proportion that had taken oral contraceptives was identical (30 percent). Fourteen parents admitted to ingesting LSD prior to conception. None of their 14 children were chromosomally abnormal.

At least 0.5 percent of newborns possess major chromosome abnormalities which are likely to impair their effectiveness as individuals in various degrees. All autosomal trisomies are associated with significant mental retardation. Although the survival rate of children with autosomal trisomies is greatly decreased, the cost of hospitalization is frequently extremely high. The primary risk for the newborns with translocations lies in the increased probability of subsequent abnormal offspring. The level of risk for mental retardation or behavioral abnormality in the infants with sex chromosome aneuploidies is currently unclear, and adequate population surveys are urgently needed to provide answers. The large majority of these infants, except for those with autosomal trisomy, appear to survive into adult life, and all have survived to age 2 in the present study. It can be calculated that each year in the United States about 20,000 infants are born with a chromosome abnormality. The impact on their families and society as a whole is not trivial.

Three methods are available for reducing this population load. The first is to identify and remove factors which increase the rate of chromosome abnormalities. Public discussion and wider knowledge of the effect of maternal age (Table 3), for example, might prove partially effective. Second, these and other high risk groups, if identified, can already be offered amniocentesis and therapeutic abortion in many states. The only foreseeable totally effective means, however, is determination of the chromosome constitution of each fetus. More surveys of the type reported here are required before these possibilities can be intelligently implemented.

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References and Notes

1. H. L. Nadler, *J. Pediat.* **74**, 132 (1969).
2. H. A. Lubs and F. H. Ruddle, in *Human Population Cytogenetics*, P. A. Jacobs, W. H. Price, P. Law, Eds. (Edinburgh Univ. Press, Edinburgh, 1970).
3. L. S. Penrose, *Ann. Hum. Genet.* **27**, 295 (1964).
4. F. Sergovich, G. H. Valentine, A. T. L. Chen, R. A. H. Kinch, M. S. Smout, *New Eng. J. Med.* **280**, 851 (1969).
5. S. G. Ratcliffe, M. M. Melville, A. L. Stewart, P. A. Jacobs, A. J. Keay, *Lancet* **1970-I**, 121 (1970).
6. P. Gerald and S. Walzer, in *Human Population Cytogenetics*, P. A. Jacobs, W. H. Price, P. Law, Eds. (Edinburgh Univ. Press, Edinburgh, 1970).
7. L. Penrose, *Down's Anomaly* (Little, Brown, Boston, 1966), chap. 10.
8. R. D. Collmann and A. Stoller, *J. Ment. Defic. Res.* **13**, 13 (1969).
9. Research supported by PHS contract PH 43-67-1463 and career development award K3-Ca-19, 745.

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Contraceptives and Dysplasia: Higher Rate for Pill Choosers

Abstract. *Among women choosing the pill in preference to other contraceptive methods there is a higher rate of the cancer precursor, dysplasia of the cervix, before any possible effect of the pill.*

Prospective studies on carcinogenic potential of the contraceptive pill depend on the observation of differential development over time. For cancer, a chronic disease of relatively low incidence, it is usually necessary to follow large numbers of women free of the disease and to compare incidence rates in those exposed and not exposed to the agent. For example, in the case of cancer of the cervix, with an annual rate of 3.1 per 10,000, it has been estimated that it may be necessary to follow a sample of 60,000 women exposed to the contraceptive pill and an equal number of controls for 1 year to detect a twofold difference in incidence. Over a 10-year follow-up, the numbers in each group could be reduced to 35,000 (*1*).

An alternative approach is possible in the case of cancer of the cervix, because women with the precursor, dysplasia, are at high risk for cancer of the cervix, the annual incidence being approximately 12 percent in women under 45 years old (*2*). The size of the population to be followed can therefore be considerably reduced by studying the carcinogenic potential of the pill in women who already have the precursor, dysplasia of the cervix (*1*). Follow-up of a relatively small population can be expected to yield valid results. Furthermore, the intrauterine device (IUD) has been reported not to affect the rate of progression from dysplasia to cancer, thus making it an ideal control for the pill (*3*).

Rates for cervical cancer and for dysplasia vary inversely with socioeconomic status, and within the low-income group there is no significant racial difference in prevalence of cervical cancer (*4*). A high yield of patients with dysplasia could therefore be expected by locating the study in a low-income area.

Participants in the study are those enrolled in the family planning program of the County Health Department: they attend clinics in a low-income, inner-